Brain imaging of the cortex in ADHD: a coordinated analysis of large-scale clinical and population-based samples

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ABSTRACT

Objective: Neuroimaging studies show structural alterations of various brain regions in children and adults with ADHD, although non-replications are frequent. Our aim is to identify cortical characteristics related to ADHD using large-scale studies. **Methods:** Cortical thickness and surface area (based on the Desikan–Killiany atlas) were compared between cases (n=2246) and controls (n=1934) for children, adolescents, and adults separately in ENIGMA-ADHD, a consortium of 36 centers. To assess familial effects on cortical measures, cases, unaffected siblings, and controls in the NeuroIMAGE study (n=506) were compared. Associations of the attention scale from the Child Behavior Checklist with cortical measures were determined in a pediatric population sample (Generation-R, n=2707). **Results:** In ENIGMA-ADHD, lower surface area values were found in children with ADHD, mainly in frontal, cingulate, and temporal regions; the largest effect was for total surface area (Cohen's *d*=-0.21; p_{FDR}=<0.001). Fusiform gyrus and temporal pole cortical thickness was also lower in children with ADHD. Neither surface area nor thickness differences were found in the adolescents/adult groups. Familial effects were seen for surface area in several regions. In an overlapping set of regions, surface area, but not thickness, was associated with attention problems in Generation-R. **Conclusion:** Subtle differences in cortical surface area are widespread in children, but not in adolescents and adults with ADHD, confirming involvement of frontal cortex and highlighting regions deserving further attention. Importantly, the alterations behave like endophenotypes in families and are linked to ADHD symptoms in the population, extending evidence that ADHD behaves as a continuous trait in the population. Future longitudinal studies should clarify individual lifespan trajectories that lead to non-significant findings in adolescent/adult groups despite presence of an ADHD diagnosis.

KEYWORDS: ADHD, cortical thickness, cortical surface area, lifespan, meta-analysis, imaging

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder characterized by age-inappropriate levels of inattention and/or hyperactivity and impulsivity. ADHD occurs in around 5-7% of children and 2.5% of adults (1, 2). ADHD can negatively affect multiple aspects of daily life of patients, and represents a major public health challenge (3). Neuroimaging studies in ADHD show differences between the brains of people with ADHD and those of healthy individuals in structure (4-9), function (8, 10, 11), and connectivity (12-14), albeit with small effect sizes (9). While informative, existing studies have several major limitations. First, most ADHD neuroimaging studies have been cross-sectional and performed during childhood; studies that either consider ADHD throughout the lifespan or have a longitudinal design are rare. In one such lifespan study, we recently showed that differences in intracranial volume (ICV) and subcortical volumes between patients and healthy individuals were largely restricted to childhood (9). Furthermore, an earlier longitudinal study showed slower, delayed development of cortical thickness and surface area in children with ADHD, especially in frontal-temporal regions (15). Nonetheless, large-scale studies of cerebral cortical architecture throughout the lifespan are lacking.

A second major limitation in the neuroimaging literature is that most studies on ADHD have small sample sizes and show limited reproducibility (16). Combining data from existing research by means of meta-/mega-analysis can produce more reliable results. For ADHD, meta-/mega-analyses of structural brain phenotypes are available for subcortical structures (9, 17), but the cortex has only been assessed in meta-analyses of brain-wide voxel-based morphometry (VBM) studies (5-8). The largest VBM study (931 patients and 822 controls) reported case-control differences for anterior cingulate, medial prefrontal cortex, ventromedial orbitofrontal cortex, and the insula (8). Here, we further the field by providing the first large-scale, mega-analytic examination of cortical measures across the lifespan in ADHD. We analyzed cortical surface area and thickness separately, as recent large-scale studies show that the biological mechanisms underlying such measures overlap only partially (18). Our large sample size also provides the power needed to examine clinical factors such as common comorbid disorders.

Neuroimaging analyses of ADHD have also largely not addressed a major question: are the observed brain differences a consequence of living with the disorder, or do the brain differences reflect underlying risk for the disorder? Different study designs can help us begin to address this question. Family-based studies can indicate if cortical changes are present in unaffected siblings of cases to indicate the involvement of shared genetic and/or environmental risk factors that underlie the cortical characteristics associated with the disorder. Several family studies (e.g. (19)) suggest that at least some of the brain alterations seen in patients are

also present in their unaffected siblings and are associated with symptom severity in healthy individuals. Population-based studies can determine whether individuals with traits of ADHD show similar cortical changes to those associated with the full syndrome. The largest population study published to date (n=776 children) showed that higher levels of ADHD symptoms were associated with a thinner cortex in caudal middle frontal, temporal, and occipital regions (20). While this and similar studies (21) showed that brain alterations extend beyond the clinical disorder, no attempts have yet been made to directly assess the overlap between studies in clinical samples and the general population. Combined, family and population-based findings suggest that the brain differences seen in those with ADHD are not simply markers of the disorder, but larger studies, directly comparing brain phenotypes across different informative study designs, are needed to shed more light on this.

Here, we present a mega-analysis of cortical thickness and surface area in participants with ADHD and healthy controls across the lifespan from the ENIGMA-ADHD Working Group, a world-wide collaboration aiming to characterize the characteristics of the brain of people with ADHD. All partners used standardized methods (segmentation protocols and quality control procedures), limiting methodological heterogeneity more than in previous meta-analyses. In addition to assessing case-control differences in children, adolescents, and adults, we investigated cortical brain correlates of clinical features, assessed familiality of effects, and mapped the dimensionality of affected cortical regions in the large, independent pediatric Generation-R population study (22).

MATERIALS AND METHODS

Contributing studies

The ENIGMA-ADHD Working Group currently consists of 36 cohorts from around the world (http://enigma.ini.usc.edu/ongoing/enigma-adhd-working-group/). All cohorts have structural imaging data available for individuals with an ADHD diagnosis, and most sites also include data from healthy controls. An overview of the sites is given in **ST1**; details of image acquisition and study protocols are provided in **ST2** and **SA1**. The dataset for the cortical analysis comprised 4,180 individuals: 2,246 people with ADHD with mean age of 19.22 years (SD= 11.31), age range of 4-62 years, 74.1% males; 1,934 healthy controls with mean age of 18.05 years (SD=11.26), age range of 4-63 years, 59.8% males.

For the analysis of dimensionally-assessed ADHD traits in the general population we used data from 2,707 individuals with mean age of 10.11 (SD=0.57) years, age range of 8.5-11.9 years, 49.4% males (**ST3**) from the Generation-R cohort (22).

For all participating cohorts, approval for the analysis was available from the responsible ethics committees.

Neuroimaging

Structural T1-weighted brain MRI data were acquired and processed at the individual sites. The images were analyzed using standardized protocols to harmonize analysis and quality control processes (http://enigma.ini.usc.edu/protocols/imaging-protocols/ and **SA2**) (23-25). Fully-automated and validated neuroimaging segmentation algorithms based on FreeSurfer versions 5.1 or 5.3 were used (**ST2**). Regions based on the Desikan–Killiany atlas were segmented, which resulted in cortical thickness and surface area values for 34 left and 34 right hemisphere regions. Two whole-hemisphere values for average thickness and average surface area were also computed. For further analysis, we used the mean of the bilateral values ((R+L)/2).

The Generation-R data were collected using a single, study-dedicated MRI scanner and processed using FreeSurfer version 6.0 on a high-performance computing system (Cartesius, surfsara.nl), for scanner sequence please see **SA3**. All imaging data were visually inspected for inaccuracies in the surface-based reconstruction. Data not suitable for analysis were excluded (for a flowchart see **SF1**), providing n=2707. For a non response analysis, please see **SA4.**

Case-control differences in cortical thickness and surface area in children, adolescents, and adults

Based on the age-specificity of earlier findings (9), three age groups were assessed: children: 4-14 years, 1081 cases, 1048 controls; adolescents: 15-21 years, 432 cases, 347 controls; adults: 22-63 years, 733 cases, 539 controls. As there are marked developmental changes across the 4 to 14 year age range, we also performed supplemental analyses on age tertiles of the childhood group. For each of the age groups we determined differences between participants with ADHD and healthy controls using mixed-effect models with 'site' as a random factor in the nlme package in R. Age and sex were included as additional covariates; for the surface area analysis, intracranial volume (ICV) was also added, as surface area scales with head size (24-26). We also include analyses without ICV as a covariate given the debate over whether it should be included as a covariate (see **SA5**). To calculate Cohen's d effect size estimates, adjusting for the appropriate covariates, we used the t-statistic from the Diagnosis (ADHD=1, control=0) predictor in the equation(27). To correct for multiple comparisons, we used a false discovery rate (FDR) at q=0.05.

Split-half validation of case-control findings

To ensure stability of effects, we performed a validation of our mega-analysis in age groups with significant results. Data were split into two halves, statistically matched for age, sex, and ICV within each site. Validation was defined as $p_{FDR}<0.05$ in the first half and $p_{uncorrected}<0.05$ in the second half, with matching effect directions(28).

Exploration of the influence of sex, IQ and clinical factors on cortical regions affected in ADHD

For regions and age groups showing validated case-control differences, we examined potential effects of sex, IQ, comorbid disorders, medication use and ADHD symptoms (severity) (see details in **SA6**). Given the exploratory nature of these analyses, we report uncorrected p-values in the Results section.

Family study

Two subsets of the ENIGMA-ADHD sample (NeuroIMAGE Amsterdam and Nijmegen (29)) had collected brain data from patients (n=211), their unaffected siblings (n=175), and unrelated controls (n=120). To determine familial effects on ADHD-affected cortical regions, unaffected siblings were compared with healthy controls in those cortical regions. Levels of ADHD symptoms in the unaffected siblings had been shown to not differ from those of controls (19). Multiple comparisons correction was performed based on the effective number of independent tests (M_{eff}) (30); differences between unaffected siblings and controls were considered significant at $p<0.01$ ($M_{eff}=5$, for details please see **SA7**).

Association between ADHD symptoms and the cortex in the general population

ADHD symptoms were assessed in children from Generation-R using the Child Behavior Checklist (CBCL)(31). Both attention problems (Syndrome Scale) and ADHD problems (DSM-oriented scale) were examined for associations with surface/thickness in regions with validated case-control differences in ENIGMA-ADHD. R statistical software (version 3.3.3) was used to fit multiple linear regressions to model these associations. Primary analyses were adjusted for age at MRI scan, sex, ICV and ethnicity. In supplemental

analyses, models were additionally adjusted for non-verbal IQ, ADHD medication status, MR-scanner software version, and motion during scanning (**SA8**).

RESULTS

Case-control differences in cortical surface area and thickness in children, adolescents, and adults

In children with ADHD versus control children, lower values of cortical surface area were widespread, with 24 out of 34 regions and total surface area being smaller in patients (**Table 1, Figure 1, ST4**). The largest effect was found for total surface area: *d*= -0.21, p_{FDR}=<0.001. When the child group was further subdivided in post-hoc analyses, this effect size increased to *d*=-0.35, p_{FDR}=<0.001 in the youngest tertile (4-9 years), which comprised 317 cases and 340 controls (**ST5**). Also more generally, the youngest group showed the largest case-control differences (**ST5**). No case-control differences were found in the adolescent and adult groups (**ST6** and **ST7**; **ST8** shows combined analysis of age groups). For results of the model without ICV, please see **ST9.**

Cortical thickness was affected in four regions (fusiform, parahippocampal, and precentral gyrus and temporal pole) in children, all being thinner in patients than controls (**Table 2**, **Figure 1 and ST10**). Further subdivision of the child group retained significant effects for fusiform gyrus (*d*= -0.31, p_{FDR}=0.002) and temporal pole (*d*=-0.25, p_{FDR}=0.02) in the group of children aged 10 and 11 (356 cases, 365 controls); in younger (4-9 years) and older (12-14 years) children, effects did not survive multiple comparisons correction(**ST11**). In adolescents and adults, no case-control differences were found (**ST12** and **ST13**; **ST14** shows combined analysis of age groups).

Validation of case-control findings

The split-half validation analysis showed seven regions for surface area and two regions for thickness to be significant in both halves (**Table 1 & 2**, **ST15 & ST16**, **Figure1**). For all other regions, the direction of effects was the same in both split-halves.
Effect sizes of the validated cortical differences across the age groups are plotted in **Figure 1**, together with the effect sizes of subcortical brain volumes from our earlier work (9). Post-hoc analysis by adding the term Agegroup*Diagnosis to the main model indicated differences in effect sizes across the lifespan for surface area of the superior frontal gyrus and thickness of the fusiform gyrus (**ST17**).

Exploration of effects of sex, IQ, comorbidity, psychostimulant medication, and ADHD severity

Extending the main findings, we investigated several factors linked to ADHD, which have shown to influence brain volume in their own right. No significant interaction effects of diagnosis-by-sex were found (**ST18**). Correcting for IQ in surface area analyses only led to minor changes in the level of significance in the case-control comparisons. In all thickness analyses, IQ was a non-significant contributor (**ST19**).

For comorbidity analyses, we had information on cases of the childhood subset (n=1081) available (comorbidity *ever* versus *never,* lifetime) for almost 50% of participants (**ST20**). In total, 194 children with ADHD (39%) were ever or currently diagnosed with a comorbid psychiatric disorder. The three most frequently co-occurring disorders were oppositional defiant disorder (ODD, present in n=79 cases (16.0%)), anxiety disorders (observed in n=39 (8.6%)), and mood disorders (seen in n=13 (3.0%)). Presence versus absence of comorbid disorders did not affect cortical surface area; a nominal effect of ever being diagnosed with a comorbid psychiatric disorder was found for fusiform gyrus thickness, with a thinner fusiform gyrus in cases with an additional disorder in the past or present (**ST21**).

Current stimulant use versus no current use had a nominally significant association with surface area of two regions in frontal cortex, with those taking medication having lower surface areas (**ST21**).

Hyperactivity/impulsivity severity ratings on Conners' questionnaires, available for n=240 childhood patients, but not inattention, showed nominally significant correlation with surface area in rostral anterior cingulate cortex (r=-0.18, p=0.01), superior frontal gyrus (r=-0.19, p=0.01), and with total surface area (r=-0.15, p=0.03) (**ST22)**.

Family study

Among the validated ADHD-associated cortical features, surface area of caudal middle frontal, lateral orbital frontal, and superior frontal gyrus and the total surface area were significantly smaller in the unaffected siblings as compared with controls (**Figure 2**, **ST23**), indicating familial effects. A similar trend was seen for the majority of the other cortical measures (**SF2**).

Effects of ADHD symptoms in the general population on the validated brain phenotypes

Population-based analysis showed caudal middle frontal gyrus, middle temporal gyrus, and total surface area to be associated with the attention problems scale of the CBCL (**Table3, SF3**); higher levels of dimensional ADHD symptoms were associated with smaller surface areas. No associations were found with the two cortical thickness measures (**Table 3**). To ensure a linear fit was optimal and that the more severe end of the symptom continuum was not driving findings, models with quadratic and cubic symptom terms were also tested. AIC and BIC values were highly similar across models, suggesting little to no improvement over the simpler linear term (**ST24**).

Adding non-verbal IQ or ADHD medication status to the analysis model of the attention problems, did not influence results (**ST25**). Results also remained stable when we tested the effect of MRI scanner software version and image quality (**ST25**). The quantitative amount of motion in the T1-weighted scan (32) did not seem to affect analyses (**ST26**).

DISCUSSION

Here, we report the largest study to date of ADHD and cortical surface area and thickness in clinical samples and a pediatric population sample. Compared with healthy controls, children with ADHD showed smaller surface area in frontal, temporal, and cingulate regions, with the effects being most prominent in the youngest children (4-9 years). Case control differences had small effect sizes, but survived validation. Differences in thickness were limited to the temporal pole and fusiform gyrus, which were thinner in children with ADHD. These differences were most prominent in the group aged 10 and 11 years. The influence of comorbidity and symptom ratings, available from subsamples, appeared limited. None of these covariates of interest showed effects surviving multiple testing correction. There were no significant associations between cortical alterations and either stimulant treatment or IQ. Family-based analyses revealed familial effects for four surface area regions, but not for any thickness measures. A set overlapping with family-based analyses (caudal middle frontal gyrus, total surface area) and/or severity rating analyses (total surface area) showed associations with CBCL-based ratings of attention problems, in the population-based sample; no such effects were found for thickness.

The regions affected in ADHD were widespread across the cortex. The frontal cortex differences in orbital, middle, and superior regions nicely confirmed earlier work (e.g. (8, 15)). These regions are important in cognitive processes related to reward and punishment, emotional processing, response inhibition, and attention - all known to be deficient in ADHD (33-35). Few studies yet have implicated structural differences in the cingulate cortex, an important structure linked to executive functioning and emotion (36), in ADHD (7, 37). Findings for the temporal cortex are particularly interesting, because both surface area and thickness were affected. The functions of this region are diverse, it seems to be involved in semantic memory, processing of abstract concepts, but also in attention, emotion processing and control (38). Integrating the current findings with our earlier subcortical results (9), the multitude of findings for brain regions involved in emotion processing is intriguing. In view of this, the network of orbito-frontal cortex, cingulate, and amygdala could be particularly interesting for future research (39, 40), as it may underlie the deficient emotional self-regulation often observed among ADHD patients (33).

Effect sizes of the observed brain differences were small, which is similar to our earlier findings for subcortical volumes and ICV in ADHD (**Figure 1**) and comparable to effect sizes seen in other psychiatric disorders studied in ENIGMA (23, 24). Whether this reflects phenotypic heterogeneity, with only a subgroup of patients showing reduced brain structure of large(r) effect size, or homogeneously small effects existing in the majority of patients remains to be investigated. Effects were not driven by IQ. Findings in several areas seemed to scale with the severity of hyperactivity/impulsivity in patients, but the heterogeneity of assessment instruments limited the power of this analysis. As in our earlier analysis of subcortical volumes and ICV, we did not find any significant associations between psychostimulant medication and cortical dimensions, neither in case-control nor in population-based designs. However, given our observational design and reliance on legacy data, we would not want to draw any definite conclusions from those results.

Looking across the lifespan, all case-control differences were most pronounced in children and non-significant in adolescents and adults. The same phenomenon, albeit attenuated, was seen in our recent cross-sectional study of ICV and subcortical structures (9) (**Figure 1**). Post-hoc analysis of potential differences in effect sizes across the three age groups in the current study confirmed age-related attenuation of effects for several structures. Those findings are in line with an earlier longitudinal study, where case-control differences in cortical thickness observed in children attenuated with increasing age, suggesting a delayed cortical maturation (41). An alternative explanation for the age-related differences might be the existence of subgroups; the childhood patient group is likely to consist of a mix of individuals who will persist and remit in adulthood, while the adult group consists largely of persisters. We

cannot yet rule out low power as a reason for not detecting significant effects in the older subgroups, which were half the size of the children's group, and these initial findings concerning apparent differences across the lifespan should be confirmed in longitudinal studies.

The case-control differences observed in the childhood sample did not seem to be influenced by comorbidity. However, we noticed that the comorbidity rate in this subset was relatively low (39%). There could be several reasons for that. First, the sample we used in our analysis of comorbidity was very young (4-14 years), as we only focused on the subsample with significant case-control differences. The relatively young age could explain the lower than expected comorbidity rate, as children might simply not yet have developed some of the frequent comorbid psychiatric disorders (e.g. substance use disorders). In comparison, Taurines and coworkers (2010) (42) described in their review that 73% of 6-18 year olds with ADHD had one or more comorbid disorders. A second reason could lie in the fact that we are dealing with research diagnoses, in which comorbidity assessments were often limited to checking in- and exclusion criteria for a specific study aim. This is a clear limitation of dealing with legacy data from multiple different sites, where different protocols and different instruments of assessment of comorbidity and symptom severity were used. We adjusted our design accordingly and concentrated only on the three most frequent comorbidities, defining those as ever or never experienced.

Although our study was not designed to study causality, our results may shed some light on the issue of whether brain differences are a consequence of living with the disorder, or are a risk factor for the disorder. Our family analysis showed unaffected siblings of cases, i.e. those without a diagnosis and with levels of ADHD symptoms comparable to healthy controls, to have similar surface area differences from controls as their affected siblings. In addition, the relationship between ADHD symptoms and cortical phenotypes also held in the general population. Here, the dimensional assessment of attention problems was related to brain morphology in a linear fashion, suggesting the phenotype and underlying brain morphology to be independent of clinical diagnosis, operating along a continuum. The two different approaches show cortical alterations in ADHD-related regions to occur independent of diagnosis. The overlap between the findings from the different approaches was, however, not complete. Future studies could perform more direct comparisons between case-control and population samples using e.g. conjunction analysis (43). The two different approaches show cortical alterations in ADHD-related regions to occur independent of diagnosis, indicating that they are neither necessary nor sufficient to cause the disorder. The overlap between the findings from the different approaches was, however, not complete. Future studies could perform more direct comparisons between case-control and population samples using e.g. conjunction analysis

(41). In such a design it would be interesting to test the liability-threshold model, to better understand which factors contribute to liability for the disorder. Also, whether the observed brain differences relative to controls are indeed risk factors for ADHD, remains to be investigated in prospective longitudinal designs. Future imaging genetics studies might further clarify the neurobiological pathways and mechanisms underlying cortical differences in ADHD. While genetic information is not available in sufficient numbers from ENIGMA-ADHD, the ENIGMA Genetics Working Group recently identified genetic factors determining cortical surface area and thickness in a largely healthy population (18). Those genetic factors might in turn constitute risk factors for ADHD given recent finding of genetic overlap between the genetic contribution to ADHD and to the total surface area of the cortex. As we have recently shown for subcortical volumes and intracranial volume, further work might delineate the individual genes or gene networks underlying such genetic overlap (Klein et al., Am. J. Psychiatry, in press; see also (44)).

The current study has several strengths and limitations. Our major strength lies in the large sample sizes in both the clinical (n=4180) and population-based (n=2707) samples, along with the use of harmonized segmentation protocols, which provided unprecedented power to detect effects. Another strength is the split-half validation combined with stringent multiple comparison correction, showing that our findings – despite small effect sizes – are stable. Also, results from the population study suggest little effect of motion during scanning on our cortical regions of interest. The combination of case-control with family- and population-based designs to identify mechanisms is an additional strength. A limitation is that we relied on legacy data in ENIGMA-ADHD, so the participating studies differ somewhat in their aims, methods, and assessments. Given this heterogeneity, our findings might underestimate the true effects, and we may have missed effects of comorbidity, medication, and symptom severity due to insufficient power. The limited sample size of the family study together with the small effect sizes for brain differences is probably the reason why the results of the family study found the expected staircase effect, at a trend level only.

In light of the findings from the current and the earlier (9) ENIGMA studies of ADHD, what should future neuroimaging studies in ADHD look like? Effect sizes observed are small (i.e. Cohen's *d*=-0.21), with largest effects for measures of total brain volume and surface area in this and our previous study (9). Also, effects are restricted to childhood despite persistent ADHD diagnosis in adolescents and adults. Future studies should answer the question, whether (regional) effect sizes are comparable in everyone, or whether subgroups exist, in which certain regional effect sizes are more pronounced. This could be examined using clustering algorithms, such as community detection, and machine learning (45). An analysis of particular interest would be the comparison between children who remit in adulthood and those who persist. In-depth analysis of adult persisters versus remitters could add to our understanding of the null findings in adults, as it seems counterintuitive that the persisters, believed to be more severely

affected, show no apparent signs of brain differences in adulthood, but the mixed group of remitters and persisters in the childhood group does. Subgroups may also provide information on comorbidity and links to symptom severity in the different behavioral domains of ADHD. Most importantly, longitudinal studies are needed to study the processes that lead to the apparent reductions of case-control effects from childhood to adolescence and adulthood; only very few longitudinal samples for ADHD are currently available (15, 29). We should also not forget that the segmentation used in the current study is based on classical neuroanatomical divisions rather than a partitioning based on biological functions (44, 46). Other cortical phenotypes such as gyrification (47), or more sophisticated methods to define regional gray matter structure, and analyses of other brain measures to be captured by neuroimaging in large sample sizes (e.g., white matter integrity (48); resting state functional MRI (49)) may help us find the presumed case-control differences in adults (50, 51).

In conclusion, we identify, for the first time, cortical phenotypes affected in ADHD that are robust, and show an association with ADHD beyond narrowly-defined clinical diagnoses. Our work suggests them to behave as endophenotypes and extends the evidence for ADHD as a continuous trait in the population from behavioral measures and genetics (52) to neuroimaging phenotypes. Future studies should clarify individual lifespan trajectories and identify the underlying genetic and environmental factors shaping these trajectories.

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FIGURE LEGENDS

FIGURE 1. Subcortical and cortical brain differences across the lifespan.

A. Displayed on the y-axis are the Cohen's *d* effect sizes with error bars showing the 95% confidence intervals for case-control differences in ENIGMA-ADHD cortical and subcortical structural features stratified by age group: children of 14 years of age and younger, adolescents from age 15 to 21 years, and adults older than 21 years. All regions displayed showed significant case-control differences in children; in analyses of cortical and subcortical features, no significant effects were seen in adolescents or adults. This is reflected in the effects sizes shown, all of which are significant for children but not for adolescent and adult groups, except for the hippocampus, which shows significance also in the adolescent group. **B**. Displayed are the heatmaps of validated case-control differences in the childhood subset for both surface area (left) and thickness (right) in both hemispheres.

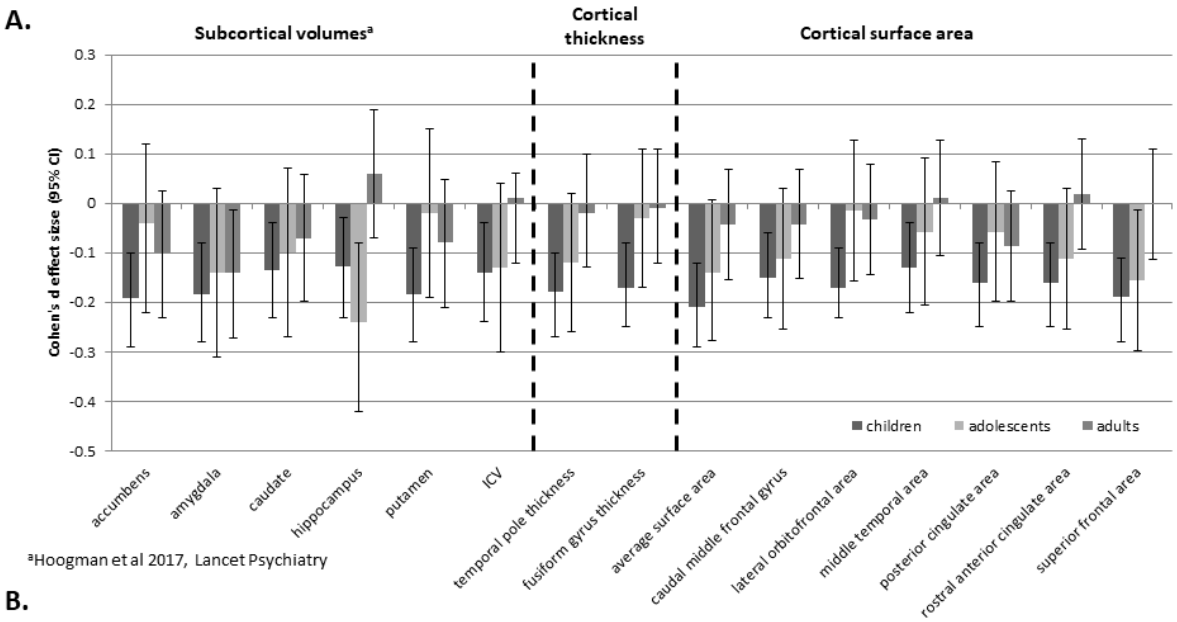


FIGURE 2. Bar graphs showing results of familiality analyses in the ADHD-affected cortical regions in the NeuroIMAGE datasets (n=506). Displayed are the cortical surface areas showing effects of familiality in the NeuroIMAGE datasets. For these regions, unaffected siblings differed from healthy controls (M_{eff}-corrected results). Cortical values are adjusted for age, gender, ICV and site.

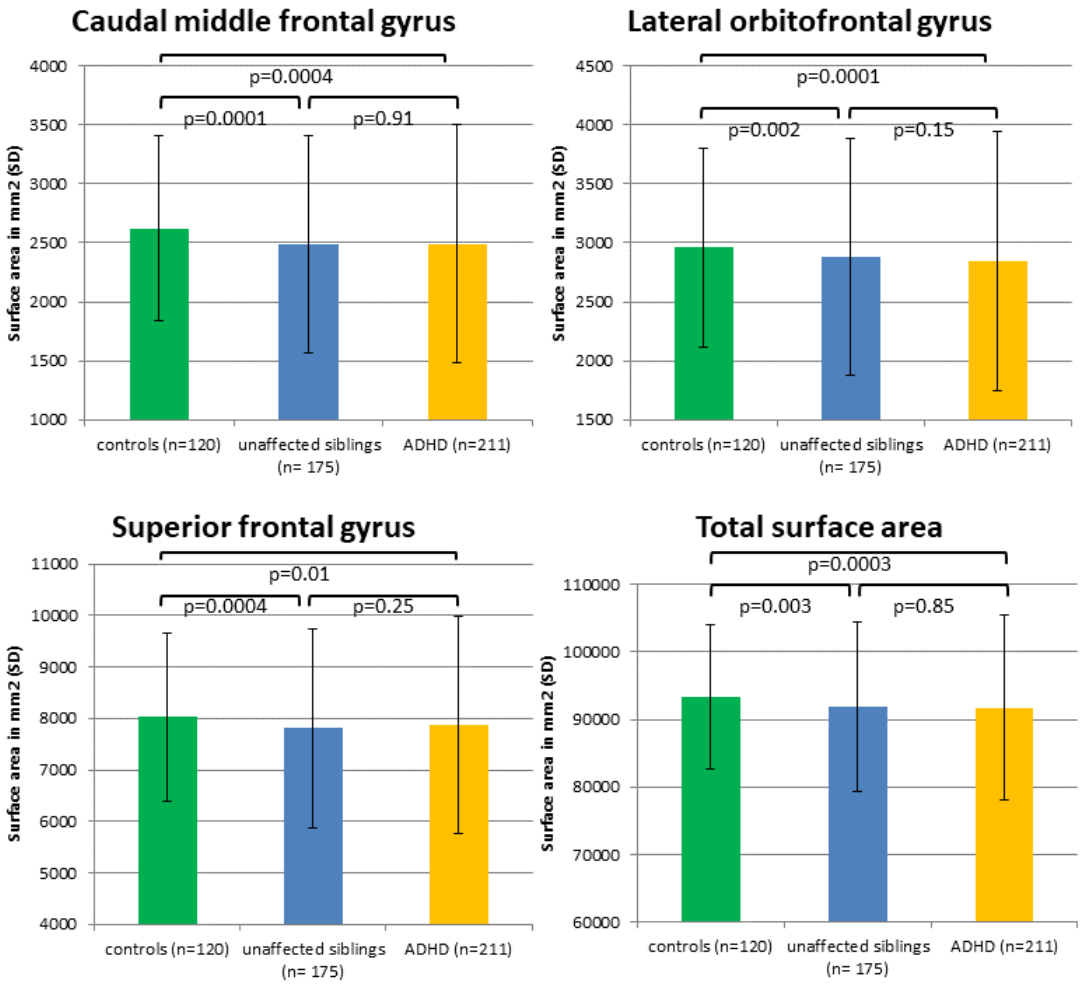


Table 1. Mega-analysis of case-control cortical surface area differences in children of 14 years of age and younger in ENIGMA-ADHD.

Cortical region	Controls (N)	ADHD (N)	Cohen's *d* (standard error)	95% confidence interval	p-value	FDR p-value
total surface area[a]	1048	1081	-0.21 (0.04)	-0.29 to -0.12	<0.001	<0.001
superior frontal gyrus[a]	1044	1074	-0.19 (0.04)	-0.28 to -0.11	<0.001	<0.001
lateral orbitofrontal cortex[a]	1047	1081	-0.17 (0.04)	-0.26 to -0.09	<0.001	<0.001
medial orbitofrontal cortex	1039	1070	-0.16 (0.04)	-0.24 to -0.07	<0.001	0.002
posterior cingulate cortex[a]	1042	1078	-0.16 (0.04)	-0.25 to -0.08	<0.001	0.002
rostral anterior cingulate cortex[a]	1041	1067	-0.16 (0.04)	-0.25 to -0.08	<0.001	0.002
superior temporal gyrus	987	993	-0.15 (0.05)	-0.24 to -0.07	<0.001	0.003
caudal middle frontal gyrus[a]	1046	1077	-0.15 (0.04)	-0.23 to -0.06	<0.001	0.003
fusiform gyrus	1043	1075	-0.13 (0.04)	-0.21 to -0.04	0.004	0.01
isthmus cingulate cortex	1040	1079	-0.13 (0.04)	-0.22 to -0.05	0.002	0.008
middle temporal gyrus[a]	1001	1024	-0.13 (0.04)	-0.22 to -0.04	0.004	0.01
rostral middle frontal gyrus	1044	1079	-0.13 (0.04)	-0.21 to -0.04	0.004	0.01
supramarginal gyrus	1036	1063	-0.13 (0.04)	-0.22 to -0.05	0.002	0.008
inferior parietal cortex	1041	1078	-0.12 (0.04)	-0.20 to -0.03	0.009	0.02
inferior temporal gyrus	1041	1064	-0.12 (0.04)	-0.21 to -0.04	0.005	0.01
lateral occipital cortex	1047	1078	-0.12 (0.04)	-0.21 to -0.04	0.005	0.01
precuneus	1044	1080	-0.12 (0.04)	-0.20 to -0.03	0.008	0.02
superior parietal cortex	1045	1073	-0.12 (0.04)	-0.21 to -0.04	0.004	0.01
insula	1042	1078	-0.12 (0.04)	-0.21 to -0.04	0.006	0.01
banks of superior temporal sulcus	974	999	-0.10 (0.05)	-0.19 to -0.01	0.02	0.04
pars triangularis of inferior frontal gyrus	1048	1074	-0.10 (0.04)	-0.18 to -0.01	0.02	0.04
postcentral gyrus	1032	1060	-0.10 (0.04)	-0.18 to -0.01	0.03	0.05
precentral gyrus	1041	1064	-0.10 (0.04)	-0.19 to -0.02	0.02	0.03
temporal pole	1043	1075	-0.10 (0.04)	-0.18 to -0.01	0.03	0.04

Note: Displayed are the significant regions surviving correction for multiple comparisons with FDR q-value<0.05. Regions are sorted based on the effect size of the difference between cases and controls (Cohen's *d*), with the regions with the largest effects on top. Regions are the average of left and right hemisphere surface area. Model is adjusted for age, sex, intracranial volume (ICV), and site. [a]regions surviving validation (see also **ST15**). For the full results please see **ST4**.

Table 2. Mega-analysis of case-control cortical thickness differences in children of 14 years of age and younger in ENIGMA-ADHD.

	Controls (N)	ADHD (N)	Cohen's *d* (standard error)	95% confidence interval	p-value	FDR p-value
temporal pole[a]	1042	1075	-0.18 (0.04)	-0.27 to -0.10	<0.001	0.001
fusiform gyrus[a]	1044	1077	-0.17 (0.04)	-0.25 to -0.08	<0.001	0.003
precentral gyrus	1040	1064	-0.16 (0.04)	-0.25 to -0.07	<0.001	0.003
parahippocampal gyrus	1041	1076	-0.15 (0.04)	-0.23 to -0.06	<0.001	0.008

Note: Displayed are the significant regions surviving correction for multiple comparisons with FDR q-value<0.05. Regions are sorted based on the effect size of the difference between cases and controls (Cohen's *d*), with the regions with the largest effects on top. Regions are the average of left and right hemisphere thickness measures. Model is adjusted for age, sex and site. [a]regions surviving validation (see also **ST16**). For the full results please see **ST10**.

Table 3. Associations between validated cortical regions and CBCL syndrome scale attention problems in Generation-R.

Cortical region	B	SE	CI lower	CI upper	β	p-value	FDR p-value
Surface area							
caudal middle frontal gyrus	**-14.10**	**5.49**	**-24.87**	**-3.33**	**-0.04**	**0.01**	**0.03**
lateral orbitofrontal cortex	-8.28	5.01	-18.10	1.54	-0.02	0.10	0.11
middle temporal gyrus	**-13.63**	**5.86**	**-25.12**	**-2.14**	**-0.03**	**0.02**	**0.04**
posterior cingulate cortex	-5.02	2.42	-9.77	-0.27	-0.03	0.04	0.06
rostral anterior cingulate cortex	-3.50	1.93	-7.29	0.29	-0.03	0.07	0.09
superior frontal gyrus	-7.16	11.93	-30.55	16.24	-0.01	0.55	0.55
total surface area	**-323.79**	**77.50**	**-475.75**	**-171.82**	**-0.04**	**<0.001**	**<0.001**
total surface area (residualized*)	**-291.62**	**77.43**	**-443.44**	**-139.79**	**-0.07**	**<0.001**	**<0.001**
Thickness							
fusiform gyrus	0.004	0.002	0.000	0.01	0.04	0.05	0.054
temporal pole	0.01	0.01	-0.001	0.03	0.04	0.07	0.07

Note: Regions are the average of left and right hemisphere surface area, and are the regions showing significant group differences in split-half analyses (**ST15** and **ST16**). Model is adjusted for age, sex, and ethnic background. ICV is also included as a covariate in the surface area analysis. B is the unstandardized regression coefficient for the square root transformed CBCL syndrome scale attention problems score, and CI is the 95% confidence interval of that regression coefficient. β is the standardized regression coefficient. *Given the high correlation between total surface area and ICV, we also tested a model where total surface area was first regressed on ICV, and the resulting residuals were used in the model described above, but without entering ICV. This shows that multicolinearity is not driving the effects. p-values in bold are considered significant, surviving correction for multiple comparisons with FDR q-value<0.05.

Data supplement to Hoogman *et al.* 'Brain imaging of the cortex in ADHD: A coordinated analysis of large-scale clinical and population-based samples'.

SA1 Study protocols of contributing sites

WürzburgADHD
The aim of the study was to investigate emotion processing in adults with ADHD. ADHD patients were inpatients or outpatients of the Department of Psychiatry and Psychotherapy. They were specifically referred to us for ADHD diagnostic assessment and treatment. Control participants were recruited via advertisements. For patients, inclusion criteria were adult and childhood ADHD according to the DSM-IV, controls had to be free of any psychiatric diagnosis. Exclusion criteria were: Age under 18 and over 60 years, IQ level below 80, severe somatic disorders, hearing problems, alcohol consumption, or self-reported drug consumption before the experiment. Controls were also excluded if they had a life-time or current SCID-I or SCID-II diagnosis or when they scored on more than two ADHD items of inattentiveness or hyperactivity according to DSM-IV. Except for 7 patients, all other patients were free from any ADHD-specific medication for at least four days.

Dublin1
The aim of the study was to investigate differences in brain structure and function in a sample of adults with ADHD, who were diagnosed with ADHD during childhood and who already took part in a genetics study at time of diagnosis. Years later during adulthood, we were able to assess psychopathology, neuropsychology and functional and structural MRI, in order to see whether adults with persistent ADHD symptomatology differ from those who do not fulfill the diagnostic criteria anymore. Moreover, a group of healthy comparison subjects was recruited from the local community, most of them by directly contacting them while they were walking along Trinity College in the city center. Healthy controls were matched for age and gender. Both patients and controls were rated using the Conners Adult ADHD scale (CAARS) (rater version), the self-rated versions of the CAARS, the Wender Utah Rating Scale (WURS), the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI). Collateral history, school certificates, ADHD
ratings and neuropsychological investigations were used when necessary. Exclusion criteria were: neurological injury or disease, comorbid psychiatric disorder (including current alcohol or substance dependency), or a history of corticosteroid medication use. IQ lower then 80.

Dublin2
The goal of the study was to investigate the hypothesis that adult ADHD patients exhibit smaller grey/white matter volumes compared to healthy controls. Moreover, we investigated the association between volumetric abnormalities and symptoms of ADHD. ADHD patients were diagnosed according to the diagnostic criteria of DSM-IV. Patients were rated using the Conners Adult ADHD scale (CAARS) (rater version), the self-rated versions of the CAARS, the Wender Utah Rating Scale (WURS), the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI). Moreover, healthy controls were recruited from the local community. Collateral history, school certificates, ADHD ratings and neuropsychological investigations were used when necessary.Exclusion criteria were: neurological injury or disease, comorbid psychiatric disorder (including current alcohol or substance dependency), or a history of corticosteroid medication use. IQ lower then 80.

ADHD Mattos
The aim of the study was to investigate reward processing in young adults with ADHD according to the Dopamine Transfer Deficit Hypothesis in a non-clinical sample. Functional magnetic resonance imaging (fMRI) was used to investigate striatal responses to reward-predicting cues and reward delivery in a classical conditioning paradigm. ADHD and matching control subsamples were recruited from the same classes. University students were initially screened with ASRS. All positive ones and a corresponding number of negative screened ones were then invited for a semi-structured interview using K-SADS adapted for adults. MINI-Plus was used to investigate comorbidity with Anxiety Disorders, Mood Disorders and Eating Disorders. Alcohol and Drugs were investigated with ASSIST. Exclusionary criteria for this study were: Current Depression, Bipolar Disorder, Psychosis, alcohol abuse and drug use, any neurological disorder, IQ lower than 80. Most individuals were treatment naive and those under meds had a 48h washout period. It was a single-site study, from a subsample of a larger study comprising 700 individuals.

ADHD200KKI
Psychiatric diagnoses were based on evaluations with the Diagnostic Interview for Children and Adolescents, Fourth Edition (DICA-IV, 1997), a structured parent interview based on DSM-IV criteria; the Conners' Parent Rating Scale-Revised, Long Form (CPRS-R), and the DuPaul ADHD Rating Scale-IV(Reid, 1998). Intelligence was evaluated with the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) and academic achievement was assessed with the Wechsler Individual Achievement Test-II [Wechsler, 2002]. All study participants were between 8.0 and 11.0 years, and had a Full Scale IQ of 80 or higher. They had no history of language disorder or a Reading Disability (RD) either screened out before a visit or based on school

assessment completed within 1 year of participation. RD was based on a statistically significant discrepancy between a child's FSIQ score and his/her Word Reading subtest score from the Wechsler Individual Achievement Test-II [Wechsler, 2002], or a standard score below 85 on the Word Reading subtest, regardless of IQ score. Participants with visual or hearing impairment, or history of other neurological or psychiatric disorder were excluded.Children assigned to the ADHD group met criteria for ADHD on the DICA-IV and either had a T-score of 65 or greater on the CPRS-R Long Form (DSM-IV Inattentive) and/or M (DSM-IV Hyperactive/Impulsive) or met criteria on the DuPaul ADHD Rating Scale IV (six out of nine items scored 2 or 3 from Inattention items and/or six out of nine scored 2 or 3 from the Hyperactivity/Impulsivity items). Children with DSM-IV diagnoses other than Oppositional Defiant Disorder or Specific Phobias were excluded. Typically developing children were required to have T-scores of 60 or below on the DSM-IV Inattention (L) and DSM-IV Hyperactivity (M) subscales of CPRS-R and no history of behavioral, emotional, or serious medical problems. Additionally, TDC individuals were not included if there was a history of school-based intervention services as established by parent interview, or if they met DSM-IV psychiatric disorder except specific phobia as reported on the DICA-IV.

ADHD200NYU
Psychiatric diagnoses were based on evaluations with the Schedule of Affective Disorders and Schizophrenia for Children—Present and Lifetime Version (KSADS-PL) administered to parents and children and the Conners' Parent Rating Scale-Revised, Long version (CPRS-LV). Intelligence was evaluated with the Wechsler Abbreviated Scale of Intelligence (WASI). Inclusion in the ADHD group required a diagnosis of ADHD based on parent and child responses to the KSADS-PL as well as on a T-score greater than or equal to 65 on at least one ADHD related index of the CPRS-R: LV. Psychostimulant drugs were withheld at least 24 hours before scanning. Inclusion criteria for TDC required absence of any Axis-I psychiatric diagnoses per parent and child KSADS-PL interview, as well as T-scores below 60 for all the CPRS-R: LV ADHD summary scales. Estimates of FSIQ above 80, right-handedness and absence of other chronic medical conditions were required for all children

ADHD200Peking
Study participants with the diagnosis of ADHD were initially identified using the Computerized Diagnostic Interview Schedule IV (C-DIS-IV). Upon referral for participation to the study participation, all participants (ADHD and TDC) were evaluated with the Schedule of Affective Disorders and Schizophrenia for Children—Present and Lifetime Version (KSADS-PL) with one parent for the establishment of the diagnosis for study inclusion. The ADHD Rating Scale (ADHD-RS) IV was employed to provide dimensional measures of ADHD symptoms. Additional inclusion criteria included: (i) right-handedness, (ii) no lifetime history of head trauma with loss of consciousness, (iii) no history of neurological disease and no diagnosis of either schizophrenia, affective disorder, pervasive development disorder, or substance abuse and (iv) full scale Wechsler Intelligence Scale for Chinese Children-Revised (WISCC-R) score of greater than 80. Psychostimulant medications were withheld at least 48 hours prior to scanning. All research was approved by the Research Ethics Review Board of Institute of Mental Health, Peking University. Informed consent was also obtained from the parent of each subject and all of the children agreed to participate in the study.

ADHD200OHSU
Psychiatric diagnoses were based on evaluations with the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-I) administered to a parent; parent and teacher Connors' Rating Scale-3rd Edition; and a clinical review by a child psychiatrist and neuropsychologist who had to agree on the diagnosis. Intelligence was evaluated with a three-subtest short form (Block Design, Vocabulary, and Information) of the Wechsler Intelligence Scale for Children, Fourth Edition. Children were excluded if they did not meet criteria for ADHD or non-ADHD groups (i.e. children deemed sub-threshold by the clinicians were excluded). Children were also excluded if a history of neurological illness, chronic medical problems, sensorimotor handicap, autistic disorder, mental retardation, or significant head trauma (with loss of consciousness) was identified by parent report, or if they had evidence of psychotic disorder or bipolar disorder on the structured parent psychiatric interview. Children prescribed short-acting stimulant medications were scanned after a minimum washout of five half-lives (i.e., 24-48 hours depending on the preparation). Typically developing control children (TDC) were excluded for presence of conduct disorder, major depressive disorder, or history of psychotic disorder, as well as for presence of ADHD.

UKA
The current sample was recruited from the in- or outpatient unit of the Department of Child and Adolescent Psychiatry Unit of RWTH Aachen University Hospital in Germany. Subjects were recruited within the aims of different neuroimaging studies in ADHD. All subjects were aged between 6 and 18 years, the majority were male and right-handed. In all studies, a comprehensive diagnostic assessment was performed by a senior child and adolescent psychiatrist using a semi-structured interview (KIDDIE-SADS; K-DIPS) for diagnosing mental disorders according to DSM-IV. Controls were also screened with this diagnostic instrument to rule out any psychiatric disorder. Subjects with confounding psychiatric disorders (i.e. psychosis),

with neurological disorders or with an IQ of less than 85 were excluded from the sample. All participants were screened for any contraindications against MRI prior to study inclusion. About 52% of all subjects with ADHD had previously been treated with psychostimulants. At the time of scanning, however, subjects had been free of stimulants for a minimum of 48 hours. All typically developing control subjects were medication-naive. The studies were carried out in accordance with the latest version of the Declaration of Helsinki. The study protocols were reviewed and approved by the local ethics committee. Written informed consent was obtained after providing a complete description of the study to the subjects and their parents. Subjects were compensated for their expenses.

BergenADHD

The sample was recruited from the Norwegian ADHD-project in Bergen, Norway. Since 2004, adult ADHD patients, family members and controls (total n ≈ 2000) have been recruited from all across Norway to this interdisciplinary project that is comparing clinical features and multiple biomarkers in patients and controls. All patients had been diagnosed according to ICD-10 or DSM-IV criteria for hyperkinetic disorder/ADHD by a psychiatrist or psychologist before inclusion. Controls were randomly selected from the comparison group in the Norwegian ADHD-project in the Bergen area, originally recruited from the database of the Medical Birth Registry of Norway. Details concerning the recruitment protocol are previously described (Dramsdahl et al. Front Psychiatry. 2011 Nov 23;2:65).

All participants in both groups were interviewed with the ADHD module of K-SADS (Kaufman et al., J. Am. Acad. Child Adolesc. Psychiatry 36, 980–988) adjusted to adults, administered by an experienced psychiatrist. The ADHD group included both medication naïve as well as medicated participants. The patients medicated with stimulants (n = 15) or atomoxetine (n = 1) were instructed to withhold medication 48 h prior to testing to reduce the possible influence of medication. Exclusion criteria for both groups were current severe psychiatric axis I disorder or substance abuse, epilepsy, or other neurological or physical disease with cognitive impairment. Participants with a lifetime history of developmental delay, premature birth before 34 weeks of gestational age, or IQ below 70 were neither included. To ensure as representative ADHD sample as possible, we included participants with current mild psychiatric comorbidity (anxiety disorders and mild depressive symptoms). No participant, however, reported ongoing, severe symptoms at the time for the MR scanning. Further exclusion criteria for the controls were lifetime history of ADHD, current ADHD symptoms (score >36 on ASRS-18, or >20 on one of the two subscales), or first-degree relatives (parents, children, siblings) with ADHD. Three of the controls had diagnosed specific phobia, but none had ongoing symptoms at the time of scanning.

Written informed consent was obtained from all participants after receiving detailed information about the procedure. The study was approved by the Norwegian Regional Medical Research Ethics Committee West IRB #3 (FWA00009490, IRB00001872).

SVG-Bergen

Children aged 8-12 years with symptoms of ADHD were referred to us from primary care physicians via psychiatric outpatients clinics in the municipality of Bergen, Norway. Healthy control children of the same age were recruited through five schools in the same geographic area. This study was part of a larger study for which the participants went through careful clinical characterization. Parents were offered a honorarium of 1000 NOK (about 120 USD) for the two days required for data collection.

We interviewed children and parents separately with a semi-structured DSM-IV-based interview, the Schedule for Affective Disorders and Schizophrenia for School Aged Children – Present and Lifetime Version (K-SADS-PL, 2009), (Kaufman et al., 1997). Parents filled in questionnaires, such as the BRIEF and the CBCL, and children filled in the self-reported State-Trait Anxiety Inventory for Children (STAIC), to allow for a dimensional characterization of the child's problems. The interviewers were clinical professionals, and a board of an experienced child and adolescent psychiatrist (K.J.P.) and a clinical psychologist (L.S.) confirmed the diagnoses. We included children with a DSM-IV-TR (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 1994) diagnosis of predominantly inattentive, predominantly hyperactive/impulsive, or combined subtype of ADHD in the patient group. The children were undiagnosed at the time of recruitment and had not received any treatment for ADHD (medication or other). All participants completed the Wechsler Intelligence Scale for Children – IV, which was used for estimation of IQ (Wechsler, 2003).

Exclusion criteria were prior ADHD diagnosis, prior or current use of psychotropic medication, IQ < 75, birth before the gestational age of 36 weeks, any prior seizure, a history of head trauma with loss of consciousness, a history of major neurological injury or illness, dyslexia or other developmental disorder, or a serious axis I disorder, such as a psychotic disorder, manifest bipolar disorder, or depression. All children were of Caucasian origin and native Norwegian speakers.

We obtained written consent and assent after full description of the study to the children and their parents. The study was approved by the Regional Committee for Medical and Health Science Research Ethics, Western Norway, and the Norwegian Social Science Data Services and performed according to the declaration of Helsinki.

DATLondon
The aim of this study was twofold: (1) to investigate the effect of type (real vs hypothetical) and magnitude of reward as well as of variation in dopamine genes on choice impulsivity; (2) to investigate striatal responsivity to rewards in ADHD combined type (ADHD-CT) using functional magnetic resonance imaging (fMRI), and whether it is modulated by variation in the dopamine transporter gene (DAT1). White male adolescents with a clinical diagnosis of ADHD-CT and age-, gender-, and handedness-matched controls were recruited from a larger sample who had participated in a previous study. The ADHD-CT group was part of the London subset of the International Multi-Centre ADHD Genetics (IMAGE) project. No comorbid disorder was associated with either subgroup formed by the stratification of the ADHD sample by DAT1 10/6 dosage (2 copies, 2 copies). Stimulant treatment (received by 72% of the ADHD-CT group) was discontinued at least 48 hours before testing.
As part of the International Multi-Centre Attention Deficit Hyperactivity Disorder Genetics (IMAGE) project, all participants were of European white descent. Exclusion criteria were an intelligence quotient (IQ) 70, autism, epilepsy, general learning difficulties, brain disorders, and any genetic or medical disorder associated with externalizing behaviors that might mimic attention- deficit/ hyperactivity disorder (ADHD). At the time of initial assessment (18 – 60 months before the current study; mean 43.2, SD 9.36), clinical participants had a clinical diagnosis of DSM-IV ADHD-combined subtype (ADHD-CT) confirmed through a semi-structured clinical interview using the Parental Account of Children's Symptoms (PACS) and parent and teacher ratings on the Conners' DSM-IV ADHD subscales in the diagnostic range (T-score 63). Parents completed the long form of the revised Conners' Rating Scale at the time of testing.

IMpACT-NL
The aim of the study was to investigate associations between genetic markers and brain and cognitive phenotypes in adults with ADHD and healthy controls. The ADHD patients and healthy subjects were recruited from the department of Psychiatry of the Radboud University Nijmegen Medical Centre and through advertisements. Patients were included if they met DSM-IV-TR criteria for ADHD in childhood as well as adulthood. All subjects were assessed using the Diagnostic Interview for Adult ADHD (DIVA)(Kooij 2010). This interview focuses on the 18 DSM-IV symptoms of ADHD and uses concrete and realistic examples to thoroughly investigate whether the symptom is present now or was in childhood. In order to obtain information about ADHD symptoms and impairment in childhood, additional information was obtained from parents and school reports, whenever possible. The Structured Clinical Interview for DSM-IV Criteria (SCID-I) was used for co-morbidity assessment. Assessments were carried out by trained professionals (psychiatrist or psychologists).
Exclusion criteria for participants were psychosis, addiction in the last 6 months, current major depression (assessed with SCID-I), full-scale IQ estimate less than 70 (Wechsler Adult Intelligence Scale-III), neurological disorders, sensorimotor handicaps, non-Caucasian ethnicity and medication use other than psychostimulants or atomoxetine. Additional exclusion criteria for healthy subjects were a current or past neurological or psychiatric disorder according to SCID-I. Patients who used ADHD stimulants were asked to withhold their medication 24 hours prior to testing. Subjects had to refrain from smoking prior to and during testing. This study was approved by the regional ethics committee. Written informed consent was obtained from all participants.

MGH
Purpose of the study: Data from MGH come from neuroimaging studies conducted by researchers in the Clinical and Research Program in Pediatric Psychopharmacology. These studies had overlapping methods and aimed to examine structural and/or functional brain abnormalities in individuals with ADHD.
Recruitment methods: Studies recruited ADHD subjects from referrals to psychiatric clinics at the Massachusetts General Hospital (MGH) as well as advertisements in the greater Boston area. Studies recruited control subjects through similar advertisements in the same settings and geographical area.
Inclusion and exclusion criteria: Males and females with a DSM-IIR or DSM-IV based diagnosis of ADHD between the ages of 18 and 59 were eligible for the study. ADHD and control participants were group matched to be comparable on age, socioeconomic status, sex distribution, handedness, and education. Exclusion criteria were deafness, blindness, psychosis, neurological disorder, sensorimotor handicaps, inadequate command of the English language, or a Full Scale intelligence quotient (IQ) estimate less than 80 as measured by the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler 1981). No ethnic or racial group was excluded.
All subjects who were currently taking short-acting stimulants underwent a 24 hour washout period prior to their scan.

NICHE
The aim of the study was to investigate brain development in children with ADHD compared to typically developing controls [e.g., de Zeeuw et al., 2012]. Participants were recruited through the Department of Psychiatry at the University Medical Center in Utrecht, The Netherlands, and through advertising. The Ethics Committee of the UMC Utrecht approved the study.

Written informed consent was obtained from the parents of all subjects after full disclosure of the study purpose and procedure. Children provided written and/or verbal assent. The Diagnostic Interview Schedule for Children (DISC, version IV), parent version [Shaffer et al., 2000], was administered by a qualified researcher to all parents in order to confirm or disprove (controls) the clinical diagnosis of ADHD (and other disorders) based on DSM-IV criteria. IQ was estimated using a four subtest short form of the Dutch version of the WISC-III (subtests Vocabulary, Block Design, Similarities and Object Assembly). Controls were excluded in the case of psychiatric morbidity or first-degree relatives with a history of psychiatric problems. Children with ADHD were excluded if they met DISC-IV criteria for any co-morbid disorder other than Oppositional Defiant Disorder or Conduct Disorder. In both groups, additional exclusion criteria were an IQ below 70, any major physical or neurological illnesses or the presence of metals in the body that precluded the MRI session. None of the control subjects were using any form of psychoactive medication. Children with ADHD on medication were asked not to take their medication 24 hours prior to the MRI scan.

NYU

The adult sample, after quality assurance of imaging data and matching for age and sex, consisted of 40 individuals with ADHD (age range: 18.2-52.9 years, 55% males) and 40 neurotypical (NT) comparisons (18.6-51.9 years, 55% males). Inclusion in the adult ADHD group required a clinician's DSM-IV-TR diagnosis of ADHD based on the Adult ADHD Clinical Diagnostic Scale version 1.2 and the Structured Clinical Interview for DSM-IV, Research Version, Non-patient Edition (SCID) to assess Axis I disorders. Most participants with ADHD (38 of 42) met criteria for persistent ADHD diagnosis (i.e., symptoms and impairment in childhood and adulthood), two participants for current ADHD only (i.e., meeting criteria only in adulthood), and two presented with history of ADHD in remission (i.e., symptoms in only childhood).
Inclusion as NT required absence of current Axis I diagnosis, assessed with SCID. Exclusion criteria for all participants were current evidence of autism, major depression, suicidality, substance-related disorder, obsessive compulsive disorder, conduct disorder, posttraumatic stress disorder, panic disorder, Tourette's disorder, lifetime history of psychosis or mania; general chronic medical conditions, left-handedness, or estimated full-scale IQ below 80. Comorbid disorders were present in 7 adults with ADHD. The Wechsler Abbreviated Scale of Intelligence (WASI) provided estimates of full-scale IQ in all adults. The Institutional Review Boards of the NYU School of Medicine and NYU granted ethical approval. All participants provided written informed consent. Magnetic resonance imaging data were obtained at the NYU Center for Brain Imaging.

UAB

Adult study: the aim of the study was to test whether psychostimulant medication affects brain structure within-subjects in a sample of adult ADHD patients. For this purpose, we conducted a longitudinal magnetic resonance study, comparing structural brain images from a group of adult ADHD patients before and after 3 years of psychostimulant treatment with a group of non-pharmacologically treated ADHD patients and a group of healthy controls. The ADHD patients were carefully selected by a specialized team of psychiatrists and psychologists from the outpatient Adult ADHD Program of Hospital Universitari Vall d'Hebron in Barcelona (Spain). All of them met the DSM-IV criteria for ADHD combined subtype and were right-handed.ADHD patients in the non-medicated group were those who voluntarily decided not to take medication after receiving the diagnosis. These were included on psychoeducational treatment of the Adult ADHD Program as treatment for ADHD and held regular visits with their psychiatrist during the duration of the study, they did not undergo any pharmacological nor cognitive-behavioral therapy. Exclusion criteria included comorbidity with other psychiatric diseases or personality disorders, assessed by the Structured Clinical Interview for Axis I (SCID-I) and Axis II . Participants with substance abuse disorder, including those who consumed tobacco and cannabis within the last 6 months, were also excluded. Participants with an estimated IQ lower than 80 as assessed by means of the Wechsler Adult Intelligence Scale were not included. Washout period of 24 h.
Children study: In this study, we applied functional MRI paradigms to assess the effects of short-term cognitive training on neural activity. We analyzed the neural activity of a sample of unmedicated ADHD children of the combined subtype, who were subjected to 10 daily 45-min sessions of either control or cognitive training MRI sessions were performed before and after the training period. The MRI acquisitions incorporated an fMRI paradigm of response inhibition and an fMRI paradigm of selective attention. Children diagnosed with ADHD combined subtype, referred from outpatient clinics at Vall d'Hebron hospital, were recruited for this study. All subjects met DSM-IV diagnostic criteria for ADHD combined subtype, as assessed by semistructured diagnostic interviews conducted by a team of psychologists and psychiatrists. In addition, Conner's scales were administered to both parents and teachers. Exclusion criteria comprised comorbidity with neurological disorders, other psychiatric disorders, cerebral damage, extreme prematurity and low IQ's (<80, WISC-R). The subjects had never been exposed to cognitive training, and they were either medication-naive or medication-free for at least 15 days prior to their participation.

ZICAPS

The aim of the study was to investigate the neural basis of neurofeedback training effects in children with ADHD. ADHD patients and healthy subjects were recruited through the outpatient clinic of the Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health Mannheim, as well as via local pediatricians and child psychiatrists. All participants met diagnostic criteria according to DSM-IV based on the K-SADS-PL semi-structured clinical interview (Delmo et al., 2000). Exclusion criteria were contraindications for MRI measurements, neurological disorders, left-handedness, and comorbid disorders other than oppositional defiant disorder, conduct disorder, and reading disorder. All patients who received medication underwent at least 48 hours of medication washout prior to scanning. This study was approved by the regional ethics committee. Written informed consent was obtained from all participants and their legal representatives.

Rubia ADHD

There are 2 studies scanned on the same scanner. The first aimed to compare ADHD patients under either Atomoxetine or MPH single dose or placebo during 4 executive function tasks in fMRI. Controls were included to test for normalization. The second study compared ADHD patients with ASD patients under either Fluoxetine or placebo in fMRI under 4 tasks. Controls were included to test for normalization. Participants were recruited via South London outpatient clinics. Most of the ADHD patients were medication-naïve, with the exception of 6 patients who received regular methylphenidate but had a washout of 48hrs before scanning and 2 patients who had been treated with methylphenidate in the past. We included only right-handed individuals, mostly medication-naïve, ADHD combined only, no comorbidities except ODD/CD, IQ > 80, had to score below cut-off for ASD on the SCQ. Thirty-three age-matched right-handed healthy boys were recruited through advertisement and scored below clinical thresholds on the SDQ and SCQ. Participants were excluded if they had comorbid psychiatric disorders as assessed by MDI, including learning disabilities, reading, speech or language disorder, neurological abnormalities, epilepsy, substance abuse and IQ < 70 on the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999).

Amsterdam & Nijmegen Neuroimage

The aim of the NeuroIMAGE was to investigate associations between genetic markers and brain and cognitive phenotypes in individuals with ADHD and healthy controls. The NeuroIMAGE project is the Dutch follow-up of the IMAGE cohort, which focussed on the genetics of ADHD, NeuroIMAGE extended by including MRI measures and the possibility to investigate structural and functional brain measures. All participants were assessed with a combination of a semi-structured diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version; K-SADS-PL) (Kaufman et al., 1997) and Conners' ADHD questionnaires from different informants (Conners, Erhardt, & Sparrow, 1999; Conners, Sitarenios, Parker, & Epstein, 1998a, 1998b). Information was combined using an algorithm, to create a combined symptom count from all informants. Symptom counts were created for inattentive symptoms and hyperactive-impulsive symptoms separately, as well as a total symptom count (sum of both symptom dimensions). ADHD diagnoses were based on full DSM-IV-TR (American Psychiatric Association, 2000) criteria, using the combined symptom count. Control participants were required to score ≤3 symptoms on both symptom dimensions. Criteria were slightly adapted for young adults (≥18 years), such that a combined symptom count of five symptoms was sufficient for a diagnosis (American Psychiatric Association, 2013), and ≤2 symptoms on both symptom dimensions were required for controls. Inclusion criteria for the NeuroIMAGE cohort were: age between 6 and 30 years, European Caucasian descent, IQ ≥ 70, and no known neurological or genetic disorder. Individuals with comorbid psychiatric disorders reported by parents were excluded, except for oppositional defiant disorder (ODD), conduct disorder (CD), and pervasive developmental disorder not otherwise specified (PDD-NOS), given their high co-occurrence in ADHD. The study was conducted at two test sites: the VU University Amsterdam/VU University Medical Centre in Amsterdam (NeuroImage-ADAM) and the Radboud University Medical Centre in Nijmegen (NeuroImage-NIJM).

NIH

This study aims to map brain development in children with and without ADHD. Diagnoses was based on the Parent Diagnostic Interview for Children and Adolescents, conducted by experienced clinicians. ADHD diagnoses were based on full DSM-IV-TR criteria (American Psychiatric Association, 2000). Primary exclusion criteria were a full-scale IQ of less than 80, evidence of medical or neurological disorders on examination or by clinical history, Tourette disorder, or any other axis-I psychiatric disorder requiring treatment with medication at study entry. IQ was estimated using an age-appropriate version of the Wechsler intelligence scales. The typically developing participants were part of the National Institute of Health (NIH) intramural project on typical brain development. The group was matched with the ADHD group on sex, IQ, and number of scans. The institutional review board of the National Institute of Mental Health approved the research protocol, and written informed consent and assent in the study were obtained from parents and children, respectively.

MTA

The primary aim of this multi-site neuroimaging study was to examine the relation between brain neuroanatomy and neurophysiology and substance use disorder in a sample of individuals previously diagnosed with childhood ADHD and a non-ADHD comparison sample with, and without substance use disorders. Participants were recruited from the longitudinal follow-up of the multi-site Multimodal Treatment Study of ADHD (MTA) 14- or 16-year follow-up assessments (i.e., 14 or 16 years after study enrollment in childhood). Original MTA participants included 579 children aged 7.0 to 9.9 years diagnosed in childhood with ADHD Combined Type. A local normative comparison group (LNCG, n=289) was recruited 24 months after baseline assessment to reflect the local populations from which the ADHD sample was drawn. Participants in the neuroimaging study included 87 ADHD (42 Cannabis Users and 45 Non-users) and 41 LNCG (20 Cannabis Users and 21 Non-users). Coordinators reviewed participant responses to the Substance Use Questionnaire obtained at the year 14 or 16 MTA follow-up visit and approached potential participants about the current study. Those interested were presented with the study description and additional screening questionnaires (e.g., brain injury screen). Eligible participants returned for a single session during which neuropsychological measures were completed, followed by neuroimaging. A participant was classified as a Cannabis User if he or she reported using cannabis monthly or more frequently during the previous year, and as a Cannabis Non-user if they had used cannabis <4 times during the previous year. It should be noted that the majority of participants in the Cannabis User group reported weekly or daily use in the past year. Participants were excluded if they self-reported binge drinking (drinking ≥5 drinks in a single session ≥1 time/week) as well as monthly or greater recreational use of other substances (e.g., cocaine, narcotics, hallucinogens, etc.). Other exclusionary criteria included any characteristic that would contraindicate magnetic resonance imaging (MRI) exposure, or a history of traumatic brain injury with loss of consciousness or that occurred in the past year. Participants taking psychotropic medications other than for ADHD were also excluded. All participants observed a 36-hour washout period for illicit drugs and alcohol, and a 1-hour washout period for nicotine and caffeine prior to the neuropsychological battery. All participants also observed a 24-hour washout for any other prescribed or over-the-counter medications.

OHSU

The aim of this single site longitudinal study is to characterize heterogeneity and mechanism in ADHD over development using clinical, cognitive, genetic, and brain imaging measures. Children age 7-11 were recruited from the local community via outreach to the entire region (mass mailings, advertisements). Eligibility and ADHD or non-ADHD group assignment was determined by formal research criteria and evaluation using a clinician-best-estimate, multi-stage, multi-method, multi-informant process. This evaluation was repeated approximately annually.

Participant exclusion criteria were tic disorder, psychotic disorder, bipolar disorder, autism spectrum disorder, conduct disorder, current major depressive episode, intellectual disability, other neurological illness, other chronic medical problems, sensorimotor disability, significant head trauma (with loss of consciousness), current prescription of psychotropic medications other than psychostimulants, or left-handedness. Additional exclusion for control subjects included current learning disability. Participants were also excluded if they had contraindications to MRI. Participants prescribed psychostimulant medications were scanned after a minimum washout period of five half-lives (i.e. 24–48 hours depending on the preparation). This study was approved by the institutional IRB. Written informed consent was obtained from parents of all participants, and all participants provided written informed assent.

UCHZ

The aim of this study was to investigate the major physiological markers of brain development in ADHD and control children, adolescents, and adults, using a multimodalitly (MRI/MRS/EEG) imaging protocol. The ADHD adults were recruited from the Psychiatric University Clinic Zurich, and underwent a clinical interview and screening for comorbidities by a consultant psychiatrist with expertise in adult ADHD. Exclusion criteria included major depression or current severe Axis I or II disorder, substance use disorder, autism spectrum disorder, tic disorder, or any other medical or neurological illness affecting brain function. The ADHD children were recruited by the Department of Child & Adolescent Psychiatry at the University of Zurich. The Kiddie-SADS-Present and Lifetime Version (K-SADS_PL) clinical interview was performed for all children with ADHD to ensure the diagnosis of combined ADHD and to exclude subjects with comorbidities. All patients met DSM-IV diagnostic criteria, and patients taking stimulants were asked to interrupt their medication at least 72 hours before the measurements. Written informed consent was obtained from all participants or their parents.

CAPSUZH

The Department of Child and Adolescent Psychiatry and Psychotherapy Zurich contributed children and adolescents with a diagnosis of ADHD and healthy controls matched for age, sex, IQ and handedness derived from two independent studies. The individuals with ADHD were recruited from our outpatient clinic, the healthy control group were recruited from local schools. All participants underwent a semi structured clinical interview (K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version, German version, (Kaufman et al., 1997)) and patients

with ADHD fulfilled the diagnosis of a combined inattention and hyperactivity-impulsivity subtype (DSM-IV code 314.01), corresponding to the 314.01 combined presentation according to DSM-5. Patients had to discontinue medication for at least 48 h prior to behavioural tests and neuroimaging sessions. Exclusion criteria for all subjects were IQ < 85 on the abbreviated Wechsler Intelligence Scale for Children (Waldmann, 2008), MRI contraindications, severe other psychiatric disorders such as schizophrenia, major depression, obsessive-compulsive disorder, pervasive developmental disorders, Tourette syndrome, substance abuse, primary mood or anxiety disorder (assessed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version), and autism spectrum disorders (assessed using the Social Communication Questionnaire), neurological disorders, or pre- and/or post-natal complications. Furthermore, parents rated the behavior of their children with the Conners Parent Rating Scale (Conners et al., 1998). Both studies were approved by the ethics commission of the canton of Zurich, CH and informed consent was obtained from all participants or their parents.

Russia

The study was organized in the National Medical Research Center of Children's Health of the Ministry of Health of the Russian Federation, Moscow. We recruited participants from outpatients who applied for help to the laboratory of neurology and cognitive health. Age of children was from 5 to 12 years. Diagnostics of ADHD: DSM-IV criteria, confirmation by neuropsychological examination (Luria's technique) and computer testing, which revealed indicators of impaired attention or impulsiveness. Exclusion criteria: comorbid psychiatric diseases, incl. autism, serious speech and language disorders (when they are an important cause of socialization disruption), borderline and low IQ levels (<80). Prior to the study, only 1 participant received a 2-month course of atomoxetine, the remaining participants did not receive traditional medication. Also, before the study, participants did not receive a systematic neuropsychological correction.

Olin neuropsychiatry research centre

Data from the Olin NRC came primarily from an NIMH-funded R01 multi-modal study to use neurocognitive measures of different forms of impulsivity (primarily executive-function rapid-response tests vs. reward-based laboratory paradigms) and fMRI tasks of motor response inhibition (Go/NoGo) and reward (Monetary Incentive Delay) to test ideas prompted by multiple pathway etiological theories of ADHD, e.g., Sonuga-Barke's "Dual Pathway" theory. Both ADHD and non-ADHD adolescents were recruited from both clinics and the local community. All participants underwent a standardized clinical evaluation that included K-SADS-PL diagnostic interviewing, a battery of neurocognitive tests, questionnaires of various clinical characteristics (mood, anxiety, etc.) and personality-based traits, and an MRI scan. In addition to the fMRI tasks, participants underwent MPRAGE, DTI, and a 5-minute resting state fMRI scan. Although genetic sampling was not part of the original project aims or scope of funding, NIMH permission was granted to collect saliva samples and use some of the grant award to fund exome chip typing. More recently, alternative funds were obtained to permit genotyping using a standard Illumina "Psych Chip" on a sub-sample of the cohort who had sufficient material left over to permit a new typing run (typing to be run in March 2018). As a final note, some participants come from earlier projects, either funded by the NIMH (through a K23 career development project) or from internal institutional funds. The clinical assessment battery for this small proportion would vary, as do the fMRI task battery. However, all MR scan parameters for MPRAGE, DTI, and resting state were identical.

Tübingen

The aim of the study is to investigate processing of emotions (facial expressions and prosody) in adult ADHD patients using fMRI and DTI. The adult ADHD patients (age: 18-45 years) will be recruited via the outpatient clinic of the University Hospital for Psychiatry and Psychotherapy Tübingen (about 200 adult ADHD patients per year were diagnosed in our facility during 2011-2013). Diagnosis will be established according to the DSM-IV criteria for ADHD of the combined type including at least six symptoms from both the domain of inattention as well as hyperactivity/impulsivity. To increase the diagnostic validity, reports of the parents on behaviour in childhood, school certificates (particularly from elementary school), questionnaires (Wender-Utah-Rating-Scale and ADHD-Self assessment scale) and performance tests to quantify attention deficits (Wiener Testsystem Cognitrone COG-S4, Daueraufmerksamkeit, DAUF-S1) are included in the diagnostic process. Only patients without other current psychiatric Axis-I disorders (e.g. current depressive episode or substance use disorder) as assessed by the structured clinical interview (SKID-I) will be included. Additional screening for depression and autistic spectrum disorders which might influence emotional processing will be performed using the Beck´s depression inventory (BDI-II) and the adult asperger assessment (AAA, Baron-Cohen et al., 2005). The healthy controls will be recruited by newspaper advertisements and posting notices. Only participants without past or current psychiatric disorders will be included and selected to balance for effects of age, gender, education, and verbal IQ (as measured by the Mehrwortschatz-Intelligenztest, MWT-B) for all three genotypes of *COMT*. As speech stimuli are used during fMRI, only right-handed subjects (as determined by a handedness questionnaire, Oldfield, 1971) are eligible for participation for both the patient and the control group. Other exclusion criteria are acute endangerment of self or others, IQ < 85, impaired hearing or vision abilities, severe internal or neurological diseases or psychopharmacological medication. In ADHD patients, methylphenidate will be discontinued one day before participation.

Furthermore, the usual exclusion criteria for participation in MRI studies apply (e.g., metal implants, pace makers, non-removable metal jewelry, tattoos with possible metal containing colours, and claustrophobia).

ACPU

Data from the Academic Child Psychiatry Unit (ACPU) were from studies aimed at examining the influences of brain function relating to attention. All male participants with ADHD were recruited from the ACPU clinic at The Royal Children's Hospital, Melbourne defined using the Anxiety Disorders Interview Schedule for Children (A-DISC), based on DSM-IV criteria. All ADHD participants additionally had Conners' DSM-IV total scores > 1.5 standard deviations above the mean for age and gender. If participants were taking ADHD medication they were asked to withdraw for at least 48 hrs prior to the assessment. Comorbidities of pervasive developmental disorders and epilepsy were excluded, but opposition deficit disorder and dysthymic disorder were not. Typically developing male controls were recruited through local schools and had no known psychiatric or neurological conditions. All participants had a full scale IQ >70 according to the WISC-IV. Approval was obtained from the Human Research Ethics Committee at the Royal Children's Hospital, and all participants/parents gave written informed consent. Neuroimaging data were collected from a single-site on a research-dedicated scanner at the Murdoch Children's Research Institute, The Royal Children's Hospital, Melbourne.

NICAP

The Neuroimaging of the Children's Attention Project (NICAP) is a longitudinal multimodal neuroimaging study aimed to determine how brain structure and function change over developmental stages in ADHD, and whether deviations from typical trajectories of brain development are associated with differential outcomes. The NICAP data is the baseline assessment from a community-based sample aged 9-11years recruited from 43 socio-economically diverse primary schools across Melbourne, Australia. For full details of the protocol see Silk *et al. BMC Psychiatry*, 2016. The study was funded by the National Medical Health and Research Council of Australia (NHMRC; project grant #1065895). The Human Research Ethics Committee of the Royal Children's Hospital, Melbourne approved study procedures (#34071), and parents/guardians of all participants provided written informed consent. Exclusion criteria were: intellectual disability; previous known serious medical, neurological or genetic condition; moderate-severe sensory impairments; and insufficient English to participate. Children were assessed in their usual classroom condition, therefore if prescribed medication they did not cease for the assessment. Medication history and dosage are recorded. Neuroimaging data were collected from a single-site on a research-dedicated scanner at the Murdoch Children's Research Institute, The Royal Children's Hospital, Melbourne.

Dundee

This study was conducted by the University of Dundee. The purpose of the iBOCA study was to develop a multi-voxel pattern analysis (mvpa) method of processing magnetic resonance imaging (MRI) brain scans to predict clinical response and tolerability of methylphenidate in children with attention deficit hyperactivity disorder (ADHD). ADHD participants were medication naive boys aged 10 -18 years. Inclusion criteria for ADHD subjects were a research diagnosis of ADHD by an experienced child and adolescent psychiatrist using the K-SADS-PL interview, age between 10 and 18 years, IQ > 70, no evidence of autism spectrum disorder, schizophrenia, bipolar disorder, depression, Tourette's or major neurological disorder. Health controls were boys aged 10 - 18 years. Inclusion criteria for healthy controls were, aged between 10 and 17 years, mean total clinician rated Swanson Nolan and Pelham IV Rating scale (SNAP IV) score (ADHD items) < 1.5, parent rated Strengths and Difficulties Questionnaire (SDQ) Hyperactivity Score < 6. No evidence of autism spectrum disorder, schizophrenia, bipolar disorder, depression, Tourette's or major neurological disorder. An exclusion criterion for both groups was history of previous ADHD medications.

ePOD

A 4 month double blind placebo controlled clinical trial (NTR3103) with methylphenidate to investigate the age-dependency of methylphenidate treatment on dopamine function in children and adults with ADHD. Patients were stimulant treatment-naïve boys (10-12 years old) and stimulant treatment-naïve men (23-40 years old) diagnosed as having ADHD and recruited through clinical programs at the Department of Child and Adolescent Psychiatry at Triversum (Alkmaar, the Netherlands), de Bascule Academic Center for Child and Adolescent Psychiatry (Amsterdam), and PsyQ mental health facility (The Hague). All children and adults met strict criteria for ADHD (all subtypes) according to the DSM-IV and were diagnosed by an experienced psychiatrist, which was confirmed with the Diagnostic Interview Schedule for Children (DISC-IV) and the Diagnostic Interview for ADHD in Adults (DIVA). Exclusion criteria were comorbid Axis I psychiatric disorders requiring treatment with medication at study entry, a history of major neurological or mental illness, IQ < 80, or a history of clinical treatment with drugs influencing the dopamine system (for adults before 23 years of age), such as stimulants, neuroleptics, and dopamine D2/D3 agonists. This study was approved by the Central Committee on Research Involving Human Subjects (CCMO) and the local

ethical review board. Written informed consent was obtained from all participants and parents or legal representatives. Subjects were scanned prior to randomization and were at that time point still medication naive.

Sao Paulo

The aim of the study is to report results of what, to our knowledge, is the first large multi-modal (morphometric and DTI) MRI study using a single-site sample of adult ADHD patients and applying machine learning methods to directly investigate the degree to which such neuroimaging measures discriminate individuals fulfilling diagnostic criteria for childhood-onset ADHD in adulthood, stimulant-naïve (and predominantly naïve to the use of any psychotropics), from age- and gender-matched HC. Adults aged between 18-50 years presenting symptoms compatible with the diagnosis of ADHD and stimulant-naïve, were recruited from two sources: the screening service of the outpatient ADHD clinic (PRODATH) of the Institute of Psychiatry, University of São Paulo, Brazil; and a pool of individuals who responded to advertisements in the Internet and other media channels (local radios and newspapers). Potentially eligible subjects underwent a detailed psychiatric interview using: the Structured Clinical Interview (SCID) for Diagnostic and Statistical Manual for Mental Disorders, 4th-edition (DSM-IV) (American Psychiatric Association APA, 1994); and ADHD-related items from an adapted version of the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS-E) (Grevet et al., 2005). In order to ascertain the presence of a current, full diagnosis of ADHD, the DSM-IV diagnostic criteria for ADHD (American Psychiatric Association APA, 1994) were used, as follows: (1) presence of at least six inattention items from the DSM-IV, at least six hyperactivity/impulsivity items, or both during the past six months; (2) chronic course of ADHD symptomatology from childhood into adulthood; and (3) impairment in various functionality domains due to ADHD symptoms (at work, home and in relationships with family and friends). We included all participants that reported onset of ADHD symptoms up to 12 years of age. Presence of other Axis I psychiatric diagnoses were established through the SCID. For the assessment of symptom severity, we used the Adult ADHD Self-Report Scale (ASRS-18) (Adler et al., 2006), the Global Assessment of Functioning (GAF) from DSM-IV and the Clinical Global Impression (CGI) scale (Lima et al., 2007).

Exclusion criteria were: lifetime or current history of any major psychiatric disorder, with the exception of mild depressive episodes, anxiety disorders and disruptive behavior disorders; presence of substance abuse or dependence (current and lifetime); presence of general medical or neurological disorders that could affect the central nervous system; history of mental retardation; history of head trauma with loss of consciousness; contraindications for MRI scanning. All subjects underwent MRI scanning in a 1.5T Siemens Espree system (Siemens, Erlangen, Germany). This study was approved by the local and national ethics committees. After complete description of the study to the subjects, written informed consent was obtained.

Sussex

The aim of the study was to investigate effects of stimulant medications on brain and reinforcement learning to reward and novelty in adults with ADHD and healthy controls. Adult ADHD patients were recruited from specialist clinics at Sussex Partnership NHS Foundation Trust. Assessment included semi-structured interview using the Diagnostic Interview for ADHD in Adults (DIVA), completion of the Conners' ADHD self-report long version and Wender Utah questionnaires, informant history and wherever possible review of school reports. All had DSM-IV confirmed diagnoses of ADHD. Age, sex and IQ-matched control participants were recruited through classified advertisements and university mailing lists. Participants gave written informed consent following full explanation of the experimental procedures. Local and national ethical approvals were obtained from Brighton and Sussex Medical School (14/014/HAR; 12/131/HAR) and the East of England (Hertfordshire) National Research Ethics Committee (reference: 12/EE/0256).

Exclusion criteria included past or current history of any neurological or psychiatric history, other than anxiety and/or unipolar depressive disorder currently in remission, past history of significant head injury, and current drug or alcohol abuse. Controls were additionally excluded if they had a history of serious cardiovascular conditions including cardiomyopathy, coronary artery disease, heart failure, ventricular arrhythmia or hypertension, current or recent use of monoamine oxidase inhibitors, coumarin anticoagulants, anticonvulsants or antipsychotics or a diagnosis of glaucoma. Of note, ADHD participants were routinely screened for these potential contraindications to stimulant medication at clinical assessment. Patients who used ADHD stimulants were asked to withhold their medication for the test day and 48 hours prior to testing. Further details can be found in Sethi et al., Neuroimage Clinical 2017;15:8-14 and Sethi et al., Brain 2018;141:1545-1557.

Clínic-Barcelona

The main objective of the study is to determine specific brain abnormalities and neurofunctional substrate underlying attentional processes related to ADHD inattentive-predominant subtype and ADHD combined subtype. A secondary aim is to correlate brain activity patterns with clinical and neuropsychological variables. The ADHD patients and healthy subjects were recruited from the department of child and adolescent Psychiatry and Psychology of Clinical Hospital of Barcelona. Patients were included if they met DSM-IV-TR criteria for ADHD, had an age between 8 and 16 years, were right-handed and male and medication-naïve. All subjects were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-

age Children Present and Lifetime version (K-SADs-PL) (Kauffman et al., 1997). Assessments were carried out by trained psychiatrists and psychologists. Exclusion criteria for participants were comorbidity with any axis I psychiatric disorder, including comorbidity with any reading, language or learning disorders, history of psychopharmacological treatment prior to the study and any clinical significant medical condition. This study was approved by the regional ethics committee. Written informed consent was obtained from all participants and their families.

SUPPLEMENTARY MATERIAL

SA2. ENIGMA imaging processing protocols.

All sites followed the standardized ENIGMA protocols that are publicly available on http://enigma.ini.usc.edu/protocols/imaging-protocols. In short, outliers were determined by calculating the interquartile range (IQR) for each of the values per cohort and per diagnostic group (ADHD and Controls). Values that were above or below 1.5 times the IQR were identified as an outlier, and were visually inspected (3D) by the researcher. When identified as segmentation failure, all values from the affected cortical regions were excluded from further analysis. In addition, cortical segmentations were overlayed on the subjects t1 image. Webpages were generated with snapshots from internal slices, and also with external views of the segmentation from different angles. All sites were provided with the manual on how to do judge these images, including the most common segmentation errors.

Overview of excluded subjects due to quality control per site

Site	Excluded subjects	Percentage of total sample	Site	Excluded subjects	Percentage of total sample
ACPU	0	0	*Nijmegen Neuroimage*	15	0.09
Amsterdam Neuroimage	8	0.04	*NYU*	0	0
BergenADHD	0	0	*NYUADHD200*	33	0.13
CAPSUZH	0	0	*OHSUADHD200*	24	0.21
DATlondon	8	0.13	*OHSU*	1	0
Dublin1	0	0	*Olin Neuropsychiatry Research Center*	0	0
Dublin2	0	0	*PekingADHD200*	16	0.07
Dundee	0	0	*Rubia ADHD*	6	0.08
Epod	5	0.05	*Russia*	0	0
IMpACT_NL	3	0.01	*SãoPaulo1*	0	0
ADHD200KKI	9	0.10	*Sussex*	0	0
Clinic Barcelona	0	0	*SVG Bergen*	3	0.06
ADHD Mattos	0	0	*Tübingen*	0	0
MGH	4	0.03	*UAB*	0	0
MTA	0	0	*UCHZ*	0	0
NICAP	0	0	*UKA*	3	0.02
Niche	2	0.01	*WurzburgADHD*	14	0.12
NIH	85	0.20	*ZiCAPS*	1	0.03

SA3. Scanner sequence of the Generation-R study.

The scanning protocol of the Generation-R study included a high-resolution, T_1-weigthed structural MRI scan using a coronal Inversion Recovery Fast Spoiled Gradient Recalled sequence with the following parameters: GE option BRAVO, T_R = 8.77ms, T_E = 3.4ms, T_I = 600ms, Flip Angle = 10°, Matrix Size = 220 x 220, Field of View = 220mm x 220mm, slice thickness = 1mm, number of slices = 230, ARC acceleration factor = 2.

SA4. Non-response Analysis Generation-R.

To ascertain whether the participants included in the study differed significantly from those excluded due to poor image/reconstruction quality or missing CBCL data, a non-response analysis was conducted. Children included had similar attention problems scores on the CBCL compared to those excluded ($M_{included}$ =3.12, $M_{excluded}$ =3.37, $p_{parametric}$ =0.08), and the sex distribution was the same in those included vs. excluded (X^2 =0.03, p =0.9). Children included in the study were slightly older ($M_{included}$ =10.1, $M_{excluded}$ =10.2, p <0.05), were more likely to be of Dutch ethnicity and less likely to be of non-Western ethnicity (X^2=139, p <0.05). Further, children included in the study on average had somewhat higher non-verbal IQ estimates ($M_{included}$ =103.9, $M_{excluded}$ =99.4, p <0.05).

SA5. Intracranial volume (ICV) as covariate in cortical analyses.

To keep as close as possible to the methods of the other ENIGMA working groups in order to make it easier to compare results, we decide to correct for ICV in the surface area analysis(24, 25). However, our previous work also showed an association between ADHD and ICV(9). Therefore, by correcting for ICV, we regress out a known ADHD effect. This should be taken into account when interpreting the results.

SA6. Exploration of the influence of comorbidity, psychostimulant medication, ADHD severity, IQ, and sex on cortical regions affected in ADHD.

For regions and age groups showing significant validated case-control differences, we examined potential effects of clinical features and IQ. We computed a variable for each possible comorbid disorder and scored individuals as 'ever or currently affected' or 'never affected'. For the three most frequent comorbid disorders, the effect of that particular comorbid disorder on cortical measures was assessed by adding it to the mega-analysis model in the sample of cases (e.g. cortical thickness= age+gender+site+comorbidity and cortical surface area= age+gender+site+ICV+comorbidity) (see **ST2** for comorbidity assessment instruments). The frequency of other comorbid disorders is expected to be too low to have sufficient power to detect effects.

A similar approach was followed to assess the effects of stimulant medication, except that current use of psychostimulants ('currently using stimulants' versus 'not currently using stimulants') and lifetime use ('ever used stimulants' versus 'never used stimulants') were separately rated. Methylphenidate, atomoxetine, and dexamphetamine were considered psychostimulants, and only treatment-based use (longer period of time) was counted.

Effects of ADHD symptom severity on cortical measures were analyzed in a case-only analysis for the largest sample size available for a specific assessment instrument, which was the Conners questionnaire (**ST2**). Separate correlation analyses of affected cortical brain measures and the quantitative variables 'number of hyperactivity/impulsivity symptoms' and 'number of inattention symptoms' were run, correcting for age, gender, site (and ICV for surface area).

To explore differential effects for both sexes, we added the interaction term 'Dx-by-Sex' to the main model and report the p-values of this term in the model.

We present these results as a sensitivity analysis, as it is debatable to add IQ to such analyses, knowing that lowered IQ is an intrinsic feature of ADHD(53, 54). It is common practice to include IQ in brain analysis, however, for ADHD this has been the subject of intense discussions in ADHD research. Prior work advises against correcting for IQ(53, 54), because a slightly lower IQ can be a feature of ADHD, adjusting for IQ will remove disorder effects in brain regions associated with both ADHD and IQ(55). For the sake of completeness, in sensitivity analysis we add IQ to our model, but interpreting these results comes with a warranty. To really be sure of the independence of IQ in our brain analysis would require us to perform case-control analysis across the IQ range. Because this is beyond the scope of our aims and also because we don't have full coverage of IQ data in our dataset, we are not able to perform such an analysis.

SA7. Calculation of the effective number of independent test (Meff)

Meff is a correction that takes the relatedness of variables into account, in this case the correlations of the brain phenotypes. As these are presumably correlated, it would be too stringent to use a Bonferroni correction, that would result in over correcting. Meff calculates, by making use of correlation structures, the number of independent tests. After determining this number, a Bonferroni correction is applied for this number of independent tests. For the analysis of the family data, we have sent a correlation matrix of the validated regions (ST13/14) to https://neurogenetics.qimrberghofer.edu.au/matSpD/. Our matrix of 9 variables resulted in 5 independent variables. Applying a Bonferroni correction for 5 tests results in a threshold of p=0.05/5=0.01

SA8. Motion during scanning in Generation-R.

We used a novel method for ascertaining motion during structural imaging(32). Briefly, in the phase-encode direction, signal variation (i.e., attenuation) from the outside of the head toward the edge of the field of view was quantified. The slope of the attenuation in signal propagating away from the head has been shown to be related to motion artifact. This slope, a single number representing the degree of motion in each child, was entered as a covariate in supplemental statistical analyses to assess the degree to which motion during scanning impacted results.

ST1. Overview of the participating sites in the ENIGMA-ADHD collaboration.

Sample name	Site, country of origin	N Total	N Cases (M/F)	N Controls (M/F)	Age SD
ACPU	Victoria, AUS	67	39/0	28/0	12.88±2.22
Amsterdam Neuroimage	Amsterdam, NLD	173	68/23	54/28	17.32±3.15
BergenADHD	Bergen, NOR	81	21/17	16/27	31.14±6.73
CAPSUZH	Zurich, CHE	75	26/13	21/15	12.51±2.37
DATlondon	London, GBR	56	27/0	29/0	15.75±2.21
Dublin1	Dublin, IRL	80	30/9	32/9	22.55±5.81
Dublin2	Dublin, IRL	20	16/4	0/0	33.65±10.15
Dundee	Dundee, GBR	45	16/6	10/13	12.89±1.84
Epod	Amsterdam, NLD	92	92/0	0/0	19.60±9.27
IMpACT_NL	Nijmegen, NLD	274	57/80	55/82	34.95±11.24
ADHD200KKI	Baltimore, USA	85	14/6	39/26	9.78±1.26
Clinic Barcelona	Barcelona, SPA	73	52/0	21/0	11.52±2.29
ADHD Mattos	Rio de Janeiro, BRA	31	21/10	0/0	24.45±2.92
MGH	New York, USA	144	41/36	28/39	35.71±12.03
MTA	Irvine, USA	129	73/15	31/10	24.61±1.40
NICAP	Victoria, AUS	146	53/12	47/34	9.91±0.54
Niche	Utrecht, NLD	155	66/10	66/13	10.41±1.98
NIH	Bethesda, USA	331	111/55	110/55	11.08±3.32
Nijmegen Neuroimage	Nijmegen, NLD	158	82/38	23/15	17.09±3.28
NYU	New York, USA	80	22/18	22/18	31.62±9.48
NYUADHD200	New York, USA	228	94/35	48/51	11.61±2.96
OHSUADHD200	Oregon, USA	89	19/7	28/35	9.28±1.33
OHSU	Oregon, USA	229	81/39	59/50	9.63±1.58
Olin Neuropsychiatry Research Center	Hartfort,USA	181	59/14	58/50	15.15±1.82
PekingADHD200	Peking, CHN	229	80/11	79/59	11.70±1.99
Rubia ADHD	London, GBR	71	41/0	30/0	14.11±2.25
Russia	Moskou, RUS	10	8/2	0/0	8.60±1.17
SãoPaulo1 - Estado	Sao Paulo, BRA	147	57/24	44/22	27.19±5.68
Sussex	Sussex, GBR	60	19/11	19/11	33.15±9.46
SVG Bergen	Bergen, NOR	51	19/4	20/8	10.06±1.33
Tübingen	Tübingen, GER	28	22/6	0/0	28.32±7.01
UAB	Barcelona, SPA	198	82/21	64/31	25.80±13.02
UCHZ	Zurich, CHE	78	20/19	21/18	22.86±14.65
UKA	Aachen, GER	145	90/7	24/24	11.13±2.75
WurzburgADHD	Würzburg, GER	107	30/25	24/28	40.21±11.31
ZiCAPS	Mannheim, GER	34	17/4	7/6	12.71±1.40
Total		**4180**	**1665/581**	**1157/777**	**18.68±11.30**

eTABLE 2. Additional information on procedures and methods at the participating sites.

Sample	Reference	Free-Surfer version	Field strength of the MRI scanner	Medication withheld during imaging	Washout period medication before imaging	Classification system for diagnosis	Instrument for co-morbidity assessment	Instrument for symptom rating	IQ instrument
Wurzburg ADHD	Conzelmann et al., Biol Psychiatry 2009	5.3	1.5 Tesla	Partly	hours to days	DSM-IV	SCID1	DSM-IV interview	MWT-B
Dublin1	McCarthy et al., JAMA Psych 2013	5.3	3 Tesla	Yes	48 h	DSM-IV	SCID1	Conners Adult ADHD rating scale observer	Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed subtests of WAIS-IV
Dublin2	Frodl et al., 2010 Amico et al., 2011	5.3	1.5 Tesla	No	no washout	DSM-IV	SCID1	Conners Adult ADHD rating scale short version	NA
ADHD Mattos	Cocchi et al., J Neuroscience 2012	5.1	3 Tesla	Yes	48h	DSM-IV	MINI	K-SADS adapted for adults	WASI
ADHD200 KKI	http://fcon_1000.projects.nitrc.org /indi/adhd200/	5.3	1.5 Tesla	unknown	unknown	DSM-IV	NA	Conners Parent Rating Scale Revised Long version	WISC-IV
ADHD200 NYU	http://fcon_1000.projects.nitrc.org /indi/adhd200/	5.3	3 Tesla	Yes	24h	DSM-IV	NA	Conners Parent Rating Scale Revised Long version	WASI
ADHD200 Peking	http://fcon_1000.projects.nitrc. org/indi/adhd200/	5.3	3 Tesla	Yes	48h	DSM-IV	NA	ADHD rating scale	WISCC-R
Sample	**Reference**	**Free-Surfer version**	**Field strength of the MRI scanner**	**Medication withheld during imaging**	**Washout period medication before imaging**	**Classification system for diagnosis**	**Instrument for co-morbidity assessment**	**Instrument for symptom rating**	**IQ instrument**

ADHD200-OHSU	http://fcon_1000.projects.nitrc.org/indi/adhd200/	5.3	3 Tesla	Yes	24-48h	DSM-IV	KSADS	Parent/Teacher Conners rating scale 3rd edition, Parent Teacher ADHD Rating Scale K-SADS	Block Design, Vocabulary and Information subtests of WISC-IV
UKA	Vloet et al., 2010, Konrad et al., 2006, Herpertz 2008, Hubner et al., 2008, Krinzinger et al., 2011	5.3	3 Tesla	Yes	48h	ICD10/DSM-IV	K-SADS and German K-Dips	German Parental and Teacher Report on ADHD	CPM (N = 30)/WASI (N = 49)/WISC-IV (N = 14)
Bergen-ADHD	Dramsdahl et al., Front Psychiatry 2011	5.3	3 Tesla	Partly	48h	ICD-10 or DSM-IV	NA	NA	WASI
SVG Bergen	Unpublished	5.3	3 Tesla	not on medication	-	DSM-IV	K-SADS-PL	K-SADS PL	WISC-IV
DATLondon	Paloyelis et al., JAACAP 2013	5.3	3 Tesla	Yes	48h	DSM-IV	NA	NA	Vocabulary, Similarities, Picture Completion and Block Design subtests of WISC/WAIS
IMpACT-NL	Hoogman et al., AMJP 2011	5.3	1.5 Tesla	Yes	24h	DSM-IV	SCID1&2	DSM-IV interview	Vocabulary and block design subtests of WAIS
MGH	Seidman et al., Biol. Psychiatry 2011	5.1	1.5 Tesla	Yes	24h	DSM-IV	SCID1	DSM-IV interview	Vocabulary & block design of WAIS
NICHE	de Zeeuw et al , PloS One 2012	5.1	1.5 Tesla	Partly	0-24h	DSM-IV	DISC-IV	NA	Vocabulary & block design WISC-3
Sample	**Reference**	**Free-Surfer version**	**Field strength of the MRI scanner**	**Medication withheld during imaging**	**Washout period medication before imaging**	**Classification system for diagnosis**	**Instrument for co-morbidity assessment**	**Instrument for symptom rating**	**IQ instrument**
UAB	Hoekzema et al PlosOne, 2012	5.3	3 Tesla	Yes	48h	DSM-IV	NA	NA	WISC

NYU	Yoncheva et al, JAACAP, 2016	5.3	3 Tesla	Yes	24h	DSM-IV	SCID1	NA	WASI
ZICAPS	Baumeister et al, Neuroscience 2016	5.3	3 Tesla	Yes	48h	DSM-IV	ODD and CD with structured clinical interview	NA	Subscales of WISC-IV
RubiaADHD	Lim et al, Psychological Medicine 2015	5.3	3 Tesla	Yes	48h	DSM-IV	Co-morbid disorders were exclusion criteria	SDQ for Hyperactive impulsive symptoms and Conners Parent Rating scale revised for Inattentive symptoms	WASI
NeuroImage-ADAM	von Rhein et al, ECAP 2014	5.3	1.5 Tesla	Yes	48h	DSM-IV	K-SADS-PL	Algorithm Von Rhein, see *reference*	Vocabulary and block design subtest of WAIS/WISC
NeuroImage-NIJM	von Rhein et al, ECAP 2014	5.3	1.5 Tesla	Yes	48h	DSM-IV	K-SADS-PL	Algorithm Von Rhein, see *reference*	Vocabulary and block design subtest of WAIS/(WISC
NIH	Shaw et al, Biological psychiatry 2012	5.3	1.5 Tesla	Yes	36h	DSM-IV	DICA	NA	Subtests of WISC
MTA	Tamm et al, Drug and Alc. Dep 2013	5.3	3 Tesla	Yes	24h	DSM-IV	NA	NA	WISC-III full version (N = 87)/subtests of WISC-III (N = 42)
ACPU	Unpublished	5.3	3Tesla	Yes	48h	DSM-IV	DISC-IV	Conners parent long version	WISC subtest and full
Sample	**Reference**	**Free-Surfer version**	**Field strength of the MRI scanner**	**Medication withheld during imaging**	**Washout period medication before imaging**	**Classification system for diagnosis**	**Instrument for co-morbidity assessment**	**Instrument for symptom rating**	**IQ instrument**

NICAP	Silk et al, BMC Psychiatry, 2016	5.3	3 Tesla	No	-	DSM-IV	DISC-IV	NA	WASI: vocabulary, matrix reasoning
Dundee	Unpublished	5.3	3 Tesla	Not on meds	-	DSM-IV	KSADS-PL, SNAP IV	KSADS-PL	British Picture Vocabulary Scale standardised Score (proxy for verbal IQ) mean 100 SD 15
Tübingen	Unpublished	5.3	3 Tesla	naive or washout of at least 5 half-life periods concerning psychotropic drugs	-	DSM-V	SCID-I	NA	NA
Olin Research centre	Stevens et al Bio Psy: Cog Neuro, 2017	5.3	3 Tesla	Yes	24h	DSM-IV	KSADS-PL	KSADS-PL	WASI Full Scale
OHSU	Dosenbach et al Neuroimage, 2017, Karalunas, et al, 2014, Costa Dias TG, et al, 2015, Gates KM, et al, 2014, Fair DA, et al, 2013, Fair DA, et al, 2010	5.3	3 Tesla	Yes	24/48h	DSM-IV and DSM-5	KSADS-PL	NA	WISC subtests: block design, vocabulary, and information
UCHZ	Bollmann et al, Translational Psychiatry, 2015; Bollmann et al, World J. Bio Psychiatry, 2015	5.3	3 Tesla	Yes	72h	DSM-IV	KSADS-PL	adults; adult conners; children conners -3d	HAWIK
Sample	**Reference**	**Free-Surfer version**	**Field strength of the MRI scanner**	**Medication withheld during imaging**	**Washout period medication before imaging**	**Classification system for diagnosis**	**Instrument for co-morbidity assessment**	**Instrument for symptom rating**	**IQ instrument**
ADHD Russia	unpublished	5.3	3 Tesla	Not on meds	-	DSM-IV	MINI	DSM-IV interview	WISC full scale

ePOD	Bottelier et al Psy Res, 2017	5.3	3 Tesla	Naive	-	DSM-IV	children: ODD en CD met DISC. Adults: MINI Plus	DBD-RS (parents) for children; ADHD-SR for adults; CGI for both	Children: WAIS subscales Vocabulary and Block design. Adults: Dutch Adult Reading test
SãoPaulo1	Chaim et al PlosOne, 2014	5.3	1.5 Tesla	Not on meds	-	DSM-IV	SCID	NA	WASI
CAPS-UZH	Iannaccone et al ECAP, 2015	5.3	3 Tesla	Yes	48h	DSM-IV-and ICD10	K-SADS-PL	NA	WISC subtests block design, similarities, digit span
Sussex	Dipasquale et al, PlosOne, 2017	5.3	1.5 Tesla	Yes	48h	DSM-IV	NA	NA	NART
Clinic Barcelona	unpublished	5.3	3 Tesla	Naive	-	DSM-IV	K-SADS	Conners Parents' Rating Scales	Cognitive General Index (CGI) from WISC-IV

SCID: Structured Clinical Interview for DSM disorders, MINI: M.I.N.I. International Neuropsychiatric Interview, K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia; K-DIPS: Kinder Diagnostische Interview bei psychischen Störungen, DISC-IV: Diagnostic Interview Schedule for Children, K-SADS-PL; Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime; DICA: Diagnostic Interview for Children and Adolescents. SDQ: Strengths and Difficulties questionnaire. MWT-B: Mehrfachwahl-Wortschatz-Intelligenz-Test, WAIS-IV: Wechsler Adult Intelligence Scale Fourth Edition, WASI: Weschler Abbreviated Scale of Intelligence, WISC-IV: Wechsler Intelligence Scale for Children Fourth Edition, WISCC-R: Wechsler Intelligence Scale for Chinese Children-Revised, CPM: Colored Progressive Matrices, WAIS-III: Wechsler Adult Intelligence Scale Third Edition, WISC-III: Wechsler Intelligence Scale for Children Third Edition, HAWIK-IV: Hamburg-Weschsler-Intelligentztest fur Kinder-IV.

ST3. Generation R sample descriptive information (n=2707).

Demographics	**Mean ± SD / N (%)**
Age at MRI	10.11 ± 0.57
Sex (girls)	1371 (50.6)
(boys)	1336 (49.4)
non-verbal IQ	103.87 ± 14.6
Dutch ethnicity[a]	1762 (65)
Non-Western ethnicity	676 (25)
Other Western ethnicity	243 (9)
Clinical information	**Mean ± SD / N (%)**
CBCL Attention Syndrome Scale Score	3.13 ± 3.08
N Clinical Range	173 (6)
CBCL Attention DSM Scale Score	2.61 ± 2.70
N Clinical Range	260 (9)
Taking ADHD Medication	87 (3)
MRI software used	**N (%)**
DV23	200 (7)
DV24	2507 (93)

Note: CBCL clinical range is falling within the 93rd percentile for a given scale. CBCL ADHD Problems Clinical is meeting the 93rd percentile clinical criteria for either the syndrome or DSM scale. [a]N=26 cases were missing data on ethnicity.

ST4. Mega-analysis of case-control cortical surface area differences in the childhood subsample.

Cortical region	Cohen's d (SE)	95% confidence interval	N controls	N ADHD	p-value	FDR p-value
banks of superior temporal sulcus	**-0.10 (0.05)**	**-0.19 to -0.01**	**974**	**999**	**0.02**	**0.04**
caudal anterior cingulate cortex	-0.08 (0.04)	-0.16 to 0.01	1040	1079	0.08	0.10
caudal middle frontal gyrus	**-0.15 (0.04)**	**-0.23 to -0.06**	**1046**	**1077**	**<0.001**	**0.003**
cuneus	-0.06 (0.04)	-0.15 to 0.02	1046	1075	0.16	0.18
entorhinal cortex	-0.05 (0.04)	-0.13 to 0.04	1013	1031	0.31	0.33
fusiform gyrus	**-0.13 (0.04)**	**-0.21 to -0.04**	**1043**	**1075**	**0.004**	**0.01**
inferior parietal cortex	**-0.12 (0.04)**	**-0.20 to -0.03**	**1041**	**1078**	**0.009**	**0.02**
inferior temporal gyrus	**-0.12 (0.04)**	**-0.21 to -0.04**	**1041**	**1064**	**0.005**	**0.01**
isthmus cingulate cortex	**-0.13 (0.04)**	**-0.22 to -0.05**	**1040**	**1079**	**0.002**	**0.008**
lateral occipital cortex	**-0.12 (0.04)**	**-0.21 to -0.04**	**1047**	**1078**	**0.005**	**0.01**
lateral orbitofrontal cortex	**-0.17 (0.04)**	**-0.26 to -0.09**	**1047**	**1081**	**<0.001**	**<0.001**
lingual gyrus	-0.09 (0.04)	-0.17 to 0.00	1047	1081	0.04	0.06
medial orbitofrontal cortex	**-0.16 (0.04)**	**-0.24 to -0.07**	**1039**	**1070**	**<0.001**	**0.002**
middle temporal gyrus	**-0.13 (0.04)**	**-0.22 to -0.04**	**1001**	**1024**	**0.004**	**0.01**
parahippocampal gyrus	-0.04 (0.04)	-0.13 to 0.04	1040	1075	0.32	0.33
paracentral lobule	-0.07 (0.04)	-0.15 to 0.02	1047	1075	0.12	0.14
pars opercularis of inferior frontal gyrus	-0.09 (0.04)	-0.17 to 0.00	1044	1074	0.04	0.06
pars orbitalis of inferior frontal gyrus	-0.07 (0.04)	-0.16 to 0.01	1046	1081	0.10	0.12
pars triangularis of inferior frontal gyrus	**-0.10 (0.04)**	**-0.18 to -0.01**	**1048**	**1074**	**0.02**	**0.04**
pericalcarine cortex	-0.04 (0.04)	-0.13 to 0.04	1046	1079	0.35	0.35
postcentral gyrus	**-0.10 (0.04)**	**-0.18 to -0.01**	**1032**	**1060**	**0.03**	**0.05**
posterior cingulate cortex	**-0.16 (0.04)**	**-0.25 to -0.08**	**1042**	**1078**	**<0.001**	**0.002**
precentral gyrus	**-0.10 (0.04)**	**-0.19 to -0.02**	**1041**	**1064**	**0.02**	**0.03**
precuneus	**-0.12 (0.04)**	**-0.20 to -0.03**	**1044**	**1080**	**0.008**	**0.02**
rostral anterior cingulate cortex	**-0.16 (0.04)**	**-0.25 to -0.08**	**1041**	**1067**	**<0.001**	**0.002**
rostral middle frontal gyrus	**-0.13 (0.04)**	**-0.21 to -0.04**	**1044**	**1079**	**0.004**	**0.01**
superior frontal gyrus	**-0.19 (0.04)**	**-0.28 to -0.11**	**1044**	**1074**	**<0.001**	**<0.001**
superior parietal cortex	**-0.12 (0.04)**	**-0.21 to -0.04**	**1045**	**1073**	**0.004**	**0.01**
superior temporal gyrus	**-0.15 (0.05)**	**-0.24 to -0.07**	**987**	**993**	**<0.001**	**0.003**
supramarginal gyrus	**-0.13 (0.04)**	**-0.22 to -0.05**	**1036**	**1063**	**0.002**	**0.008**

frontal pole	-0.05 (0.04)	-0.14 to 0.03	1047	1081	0.21	0.23
temporal pole	**-0.10 (0.04)**	**-0.18 to -0.01**	**1043**	**1075**	**0.03**	**0.04**
transverse temporal gyrus	-0.07 (0.04)	-0.16 to 0.01	1046	1078	0.11	0.13
insula	**-0.12 (0.04)**	**-0.21 to -0.04**	**1042**	**1078**	**0.006**	**0.01**
total surface area	**-0.21 (0.04)**	**-0.29 to -0.12**	**1048**	**1081**	**<0.001**	**<0.001**

p-values in bold are considered significant, surviving correction for multiple comparisons with FDR q-value<0.05.

ST5. Mega-analysis of case-control cortical surface area differences in a tertile split of the group of children (4-14y).

	1st tertile age 4-9			2nd tertile age 10-11			3rd tertile 12-14		
	Cohen's d	**p-value**	**FDR p-value**	**Cohen's d**	**p-value**	**FDR p-value**	**Cohen's d**	**p-value**	**FDR p-value**
banks of superior temporal sulcus	**-0.19**	**0.02**	**0.04**	-0.03	0.68	0.77	-0.08	0.29	0.83
caudal anterior cingulate cortex	**-0.18**	**0.02**	**0.04**	-0.08	0.30	0.43	0.02	0.75	0.90
caudal middle frontal gyrus	-0.17	0.03	0.05	-0.11	0.14	0.36	-0.16	0.04	0.65
cuneus	-0.08	0.33	0.35	0.05	0.52	0.63	-0.14	0.07	0.65
entorhinal cortex	-0.10	0.19	0.21	-0.15	0.06	0.22	0.12	0.13	0.65
fusiform gyrus	**-0.19**	**0.02**	**0.04**	-0.12	0.11	0.30	-0.03	0.71	0.90
inferior parietal cortex	**-0.22**	**0.006**	**0.02**	-0.16	0.04	0.21	0.05	0.50	0.83
inferior temporal gyrus	**-0.20**	**0.01**	**0.03**	-0.08	0.27	0.43	-0.09	0.25	0.83
isthmus cingulate cortex	-0.16	0.04	0.06	**-0.23**	**0.002**	**0.03**	-0.02	0.75	0.90
lateral occipital cortex	-0.17	0.04	0.06	-0.09	0.26	0.43	-0.12	0.12	0.65
lateral orbitofrontal cortex	**-0.32**	**<0.001**	**0.001**	-0.15	0.05	0.21	-0.07	0.35	0.83
lingual gyrus	-0.02	0.83	0.83	-0.16	0.04	0.21	-0.06	0.42	0.83
medial orbitofrontal cortex	**-0.25**	**0.002**	**0.01**	-0.14	0.07	0.24	-0.05	0.54	0.85
middle temporal gyrus	**-0.22**	**0.008**	**0.02**	-0.08	0.31	0.43	-0.12	0.12	0.65
parahippocampal gyrus	-0.13	0.09	0.12	-0.09	0.27	0.43	0.05	0.50	0.83
paracentral lobule	-0.17	0.04	0.06	-0.05	0.48	0.60	-0.01	0.87	0.92
pars opercularis of inferior frontal gyrus	**-0.20**	**0.01**	**0.03**	-0.02	0.80	0.83	-0.07	0.32	0.83
pars orbitalis of inferior frontal gyrus	-0.12	0.13	0.15	-0.13	0.08	0.27	0.01	0.86	0.92
pars triangularis of inferior frontal gyrus	-0.13	0.11	0.13	-0.11	0.16	0.37	-0.07	0.36	0.83
pericalcarine cortex	0.03	0.67	0.69	-0.02	0.80	0.83	-0.13	0.09	0.65
postcentral gyrus	**-0.20**	**0.01**	**0.03**	-0.08	0.29	0.43	0.02	0.80	0.90
posterior cingulate cortex	-0.16	0.05	0.07	**-0.26**	**<0.001**	**0.01**	-0.05	0.47	0.83
precentral gyrus	**-0.31**	**<0.001**	**0.001**	0.03	0.72	0.78	-0.07	0.35	0.83
precuneus	**-0.24**	**0.003**	**0.01**	-0.10	0.19	0.38	0.00	0.98	0.98
rostral anterior cingulate cortex	-0.15	0.07	0.09	**-0.26**	**<0.001**	**0.01**	-0.07	0.38	0.83
rostral middle frontal gyrus	**-0.21**	**0.008**	**0.02**	-0.10	0.18	0.38	-0.05	0.49	0.83
superior frontal gyrus	**-0.29**	**<0.001**	**0.002**	-0.13	0.09	0.27	-0.15	0.04	0.65
superior parietal cortex	**-0.21**	**0.008**	**0.02**	-0.09	0.23	0.43	-0.04	0.58	0.85
superior temporal gyrus	**-0.31**	**<0.001**	**0.001**	-0.06	0.44	0.57	-0.08	0.30	0.83
supramarginal gyrus	**-0.32**	**<0.001**	**0.001**	-0.08	0.32	0.43	-0.03	0.67	0.90
frontal pole	-0.10	0.19	0.21	0.00	0.99	0.99	-0.02	0.77	0.90
temporal pole	**-0.19**	**0.02**	**0.03**	-0.16	0.04	0.21	0.04	0.58	0.85
transverse temporal gyrus	**-0.20**	**0.01**	**0.03**	-0.04	0.63	0.74	0.01	0.90	0.93
insula	**-0.26**	**0.001**	**0.005**	-0.09	0.24	0.43	-0.03	0.72	0.90
total surface area	**-0.35**	**<0.001**	**<0.001**	-0.17	0.02	0.21	-0.09	0.23	0.83

Note: the 1st tertile has 317 cases and 340 controls, the 2nd tertile has 356 cases and 365 controls, the 3rd tertile has 408 cases and 343 controls. p-values in bold are considered significant, surviving correction for multiple comparisons with FDR q-value<0.05.

ST6. Mega-analysis of case-control cortical surface area differences in the adolescent subsample.

Cortical region	Cohen's d (SE)	95% confidence interval	N controls	N ADHD	p-value	FDR p-value
banks of superior temporal sulcus	-0.01 (0.07)	-0.16 to 0.13	328	403	0.87	0.96
caudal anterior cingulate cortex	-0.14 (0.07)	-0.28 to 0	347	432	0.05	0.30
caudal middle frontal gyrus	-0.11 (0.07)	-0.25 to 0.03	345	432	0.13	0.31
cuneus	-0.1 (0.07)	-0.24 to 0.04	346	430	0.17	0.36
entorhinal cortex	-0.12 (0.07)	-0.27 to 0.02	331	414	0.10	0.31
fusiform gyrus	-0.11 (0.07)	-0.25 to 0.03	345	428	0.14	0.31
inferior parietal cortex	-0.17 (0.07)	-0.31 to -0.03	344	427	0.02	0.30
inferior temporal gyrus	0 (0.07)	-0.15 to 0.14	336	408	0.98	0.99
isthmus cingulate cortex	-0.16 (0.07)	-0.3 to -0.02	347	432	0.03	0.30
lateral occipital cortex	-0.08 (0.07)	-0.22 to 0.06	347	432	0.29	0.49
lateral orbitofrontal cortex	-0.01 (0.07)	-0.16 to 0.13	347	431	0.84	0.95
lingual gyrus	-0.05 (0.07)	-0.19 to 0.09	344	429	0.49	0.72
medial orbitofrontal cortex	-0.01 (0.07)	-0.15 to 0.13	346	430	0.91	0.96
middle temporal gyrus	-0.06 (0.08)	-0.21 to 0.09	321	389	0.46	0.70
parahippocampal gyrus	-0.03 (0.07)	-0.18 to 0.11	345	429	0.64	0.83
paracentral lobule	-0.02 (0.07)	-0.16 to 0.12	347	430	0.75	0.88
pars opercularis of inferior frontal gyrus	-0.08 (0.07)	-0.23 to 0.06	346	429	0.25	0.49
pars orbitalis of inferior frontal gyrus	-0.08 (0.07)	-0.22 to 0.06	346	432	0.27	0.49
pars triangularis of inferior frontal gyrus	-0.14 (0.07)	-0.28 to 0	347	432	0.06	0.30
pericalcarine cortex	-0.13 (0.07)	-0.27 to 0.01	347	431	0.08	0.30
postcentral gyrus	-0.04 (0.07)	-0.18 to 0.1	345	428	0.58	0.78
posterior cingulate cortex	-0.06 (0.07)	-0.2 to 0.08	347	432	0.44	0.69
precentral gyrus	-0.03 (0.07)	-0.17 to 0.11	345	426	0.66	0.83
precuneus	-0.11 (0.07)	-0.25 to 0.03	347	431	0.14	0.31
rostral anterior cingulate cortex	-0.11 (0.07)	-0.25 to 0.03	346	430	0.13	0.31
rostral middle frontal gyrus	-0.11 (0.07)	-0.25 to 0.03	347	432	0.13	0.31
superior frontal gyrus	-0.16 (0.07)	-0.3 to -0.01	347	431	0.04	0.30
superior parietal cortex	-0.18 (0.07)	-0.32 to -0.04	347	430	0.02	0.30
superior temporal gyrus	-0.03 (0.08)	-0.18 to 0.12	319	376	0.70	0.85
supramarginal gyrus	-0.04 (0.07)	-0.18 to 0.1	343	424	0.58	0.78
frontal pole	-0.11 (0.07)	-0.25 to 0.03	347	432	0.14	0.31
temporal pole	-0.13 (0.07)	-0.27 to 0.01	345	429	0.07	0.30
transverse temporal gyrus	0 (0.07)	-0.14 to 0.14	345	429	0.99	0.99
insula	-0.08 (0.07)	-0.22 to 0.06	344	428	0.30	0.49
total surface area	-0.14 (0.07)	-0.28 to 0.01	347	432	0.07	0.30

ST7. Mega-analysis of case-control cortical surface area differences in the adult subsample.

Cortical region	Cohen's d (SE)	95% confidence interval	N controls	N ADHD	p-value	FDR p-value
banks of superior temporal sulcus	0.01 (0.06)	-0.1 to 0.12	514	709	0.88	0.97
caudal anterior cingulate cortex	-0.05 (0.06)	-0.16 to 0.06	538	730	0.37	0.97
caudal middle frontal gyrus	-0.04 (0.06)	-0.15 to 0.07	539	733	0.47	0.97
cuneus	0 (0.06)	-0.11 to 0.11	539	732	0.97	0.97
entorhinal cortex	-0.01 (0.06)	-0.12 to 0.11	479	670	0.93	0.97
fusiform gyrus	-0.05 (0.06)	-0.17 to 0.07	493	687	0.41	0.97
inferior parietal cortex	0 (0.06)	-0.11 to 0.11	538	730	0.96	0.97
inferior temporal gyrus	-0.03 (0.06)	-0.15 to 0.08	493	683	0.57	0.97
isthmus cingulate cortex	0.05 (0.06)	-0.07 to 0.16	539	733	0.43	0.97
lateral occipital cortex	-0.02 (0.06)	-0.13 to 0.09	539	730	0.73	0.97
lateral orbitofrontal cortex	-0.03 (0.06)	-0.14 to 0.08	539	733	0.56	0.97
lingual gyrus	0 (0.06)	-0.12 to 0.12	494	688	1.00	0.97
medial orbitofrontal cortex	-0.05 (0.06)	-0.16 to 0.06	539	731	0.40	0.97
middle temporal gyrus	0.01 (0.06)	-0.11 to 0.13	477	670	0.86	0.97
parahippocampal gyrus	-0.16 (0.06)	-0.27 to -0.04	492	688	0.01	0.40
paracentral lobule	0.04 (0.06)	-0.07 to 0.15	538	732	0.51	0.97
pars opercularis of inferior frontal gyrus	-0.04 (0.06)	-0.15 to 0.07	539	731	0.52	0.97
pars orbitalis of inferior frontal gyrus	-0.06 (0.06)	-0.17 to 0.05	539	732	0.28	0.97
pars triangularis of inferior frontal gyrus	-0.08 (0.06)	-0.2 to 0.03	538	732	0.14	0.97
pericalcarine cortex	-0.08 (0.06)	-0.19 to 0.03	539	732	0.16	0.97
postcentral gyrus	-0.06 (0.06)	-0.17 to 0.06	528	727	0.32	0.97
posterior cingulate cortex	-0.09 (0.06)	-0.2 to 0.02	539	733	0.13	0.97
precentral gyrus	-0.01 (0.06)	-0.12 to 0.1	537	729	0.86	0.97
precuneus	-0.03 (0.06)	-0.14 to 0.09	539	732	0.66	0.97
rostral anterior cingulate cortex	0.02 (0.06)	-0.09 to 0.13	535	730	0.74	0.97
rostral middle frontal gyrus	-0.04 (0.06)	-0.15 to 0.07	538	733	0.49	0.97
superior frontal gyrus	0 (0.06)	-0.11 to 0.11	535	730	0.99	0.97
superior parietal cortex	-0.04 (0.06)	-0.15 to 0.07	539	730	0.46	0.97
superior temporal gyrus	-0.03 (0.06)	-0.15 to 0.09	476	661	0.64	0.97
supramarginal gyrus	0.01 (0.06)	-0.1 to 0.12	535	728	0.83	0.97
frontal pole	0.02 (0.06)	-0.09 to 0.13	539	733	0.71	0.97
temporal pole	-0.08 (0.06)	-0.2 to 0.03	494	688	0.17	0.97
transverse temporal gyrus	-0.07 (0.06)	-0.18 to 0.05	494	688	0.26	0.97
insula	-0.13 (0.06)	-0.25 to -0.02	532	725	0.02	0.51
total surface area	-0.04 (0.06)	-0.15 to 0.07	539	733	0.46	0.97

ST8. Mega-analysis of case-control cortical surface area differences in the total sample (children, adolescents and adults combined).

Cortical region	Cohen's d (SE)	95% confidence interval	N controls	N ADHD	p-value	FDR p-value
banks of superior temporal sulcus	**-0.07 (0.03)**	**-0.13 to 0**	**1816**	**2111**	**0.04**	**0.04**
caudal anterior cingulate cortex	**-0.09 (0.03)**	**-0.15 to -0.03**	**1925**	**2241**	**0.004**	**0.007**
caudal middle frontal gyrus	**-0.13 (0.03)**	**-0.19 to -0.07**	**1930**	**2242**	**<0.001**	**<0.001**
cuneus	-0.06 (0.03)	-0.12 to 0	1931	2237	0.05	0.05
entorhinal cortex	-0.07 (0.03)	-0.13 to 0	1823	2115	0.04	0.05
fusiform gyrus	**-0.12 (0.03)**	**-0.18 to -0.06**	**1881**	**2190**	**<0.001**	**<0.001**
inferior parietal cortex	**-0.11 (0.03)**	**-0.17 to -0.05**	**1923**	**2235**	**<0.001**	**0.002**
inferior temporal gyrus	**-0.1 (0.03)**	**-0.16 to -0.04**	**1870**	**2155**	**0.002**	**0.003**
isthmus cingulate cortex	**-0.09 (0.03)**	**-0.15 to -0.03**	**1926**	**2244**	**0.003**	**0.005**
lateral occipital cortex	**-0.11 (0.03)**	**-0.17 to -0.05**	**1933**	**2240**	**<0.001**	**0.002**
lateral orbitofrontal cortex	**-0.12 (0.03)**	**-0.18 to -0.06**	**1933**	**2245**	**<0.001**	**<0.001**
lingual gyrus	**-0.07 (0.03)**	**-0.13 to -0.01**	**1885**	**2198**	**0.03**	**0.04**
medial orbitofrontal cortex	**-0.11 (0.03)**	**-0.17 to -0.05**	**1924**	**2231**	**<0.001**	**0.001**
middle temporal gyrus	**-0.1 (0.03)**	**-0.17 to -0.04**	**1799**	**2083**	**0.002**	**0.003**
parahippocampal gyrus	**-0.08 (0.03)**	**-0.14 to -0.01**	**1877**	**2192**	**0.02**	**0.02**
paracentral lobule	-0.04 (0.03)	-0.1 to 0.02	1932	2237	0.24	0.25
pars opercularis of inferior frontal gyrus	**-0.08 (0.03)**	**-0.15 to -0.02**	**1929**	**2234**	**0.007**	**0.01**
pars orbitalis of inferior frontal gyrus	**-0.08 (0.03)**	**-0.14 to -0.02**	**1931**	**2245**	**0.009**	**0.01**
pars triangularis of inferior frontal gyrus	**-0.12 (0.03)**	**-0.18 to -0.06**	**1933**	**2238**	**<0.001**	**<0.001**
pericalcarine cortex	**-0.08 (0.03)**	**-0.14 to -0.02**	**1932**	**2242**	**0.007**	**0.01**
postcentral gyrus	**-0.1 (0.03)**	**-0.16 to -0.03**	**1905**	**2215**	**0.002**	**0.005**
posterior cingulate cortex	**-0.13 (0.03)**	**-0.2 to -0.07**	**1928**	**2243**	**<0.001**	**<0.001**
precentral gyrus	**-0.08 (0.03)**	**-0.14 to -0.02**	**1923**	**2219**	**0.01**	**0.02**
precuneus	**-0.1 (0.03)**	**-0.16 to -0.04**	**1930**	**2243**	**0.001**	**0.003**
rostral anterior cingulate cortex	**-0.11 (0.03)**	**-0.17 to -0.05**	**1922**	**2227**	**<0.001**	**0.002**
rostral middle frontal gyrus	**-0.12 (0.03)**	**-0.18 to -0.06**	**1929**	**2244**	**<0.001**	**<0.001**
superior frontal gyrus	**-0.15 (0.03)**	**-0.21 to -0.09**	**1926**	**2235**	**<0.001**	**<0.001**
superior parietal cortex	**-0.13 (0.03)**	**-0.19 to -0.07**	**1931**	**2233**	**<0.001**	**<0.001**
superior temporal gyrus	**-0.11 (0.03)**	**-0.17 to -0.04**	**1782**	**2030**	**0.001**	**0.002**
supramarginal gyrus	**-0.09 (0.03)**	**-0.15 to -0.03**	**1914**	**2215**	**0.004**	**0.007**
frontal pole	-0.05 (0.03)	-0.11 to 0.01	1933	2246	0.12	0.12
temporal pole	**-0.11 (0.03)**	**-0.18 to -0.05**	**1882**	**2192**	**<0.001**	**0.001**
transverse temporal gyrus	-0.06 (0.03)	-0.12 to 0	1885	2195	0.05	0.05
insula	**-0.12 (0.03)**	**-0.19 to -0.06**	**1918**	**2231**	**<0.001**	**<0.001**
total surface area	**-0.17 (0.03)**	**-0.24 to -0.11**	**1934**	**2246**	**<0.001**	**<0.001**

Rows in bold are considered significant, surviving correction for multiple comparisons with FDR q-value<0.05.

ST9. Mega-analysis of case-control cortical surface area differences without including ICV in the model for all age groups.

	Children			Adolescents			Adults		
Cortical region	**Cohen's d**	**p-value**	**FDR p-value**	**Cohen's d**	**p-value**	**FDR p-value**	**Cohen's d**	**p-value**	**FDR p-value**
banks of superior temporal sulcus	**-0.20**	**<0.001**	**<0.001**	-0.08	0.28	0.28	0.02	0.74	0.99
caudal anterior cingulate cortex	**-0.18**	**<0.001**	**<0.001**	**-0.20**	**0.01**	**0.04**	-0.04	0.44	0.99
caudal middle frontal gyrus	**-0.25**	**<0.001**	**<0.001**	-0.17	0.03	0.06	-0.03	0.58	0.99
cuneus	**-0.16**	**<0.001**	**<0.001**	-0.15	0.04	0.08	0.00	0.98	0.99
entorhinal cortex	**-0.13**	**0.005**	**0.005**	-0.18	0.02	0.05	0.00	0.98	0.99
fusiform gyrus	**-0.25**	**<0.001**	**<0.001**	-0.18	0.01	0.05	-0.04	0.46	0.99
inferior parietal cortex	**-0.23**	**<0.001**	**<0.001**	**-0.24**	**0.002**	**0.03**	0.01	0.86	0.99
inferior temporal gyrus	**-0.25**	**<0.001**	**<0.001**	-0.10	0.18	0.20	-0.03	0.56	0.99
isthmus cingulate cortex	**-0.24**	**<0.001**	**<0.001**	**-0.22**	**0.003**	**0.03**	0.04	0.50	0.99
lateral occipital cortex	**-0.23**	**<0.001**	**<0.001**	-0.15	0.04	0.08	-0.01	0.81	0.99
lateral orbitofrontal cortex	**-0.29**	**<0.001**	**<0.001**	-0.10	0.18	0.20	-0.03	0.66	0.99
lingual gyrus	**-0.19**	**<0.001**	**<0.001**	-0.11	0.12	0.15	0.00	0.94	0.99
medial orbitofrontal cortex	**-0.27**	**<0.001**	**<0.001**	-0.10	0.16	0.19	-0.04	0.52	0.99
middle temporal gyrus	**-0.26**	**<0.001**	**<0.001**	-0.15	0.05	0.08	0.00	0.99	0.99
parahippocampal gyrus	**-0.16**	**<0.001**	**<0.001**	-0.10	0.18	0.20	-0.14	0.02	0.65
paracentral lobule	**-0.17**	**<0.001**	**<0.001**	-0.09	0.23	0.25	0.04	0.53	0.99
pars opercularis of inferior frontal gyrus	**-0.19**	**<0.001**	**<0.001**	-0.14	0.06	0.10	-0.03	0.60	0.99
pars orbitalis of inferior frontal gyrus	**-0.18**	**<0.001**	**<0.001**	-0.15	0.05	0.08	-0.05	0.39	0.99
pars triangularis of inferior frontal gyrus	**-0.20**	**<0.001**	**<0.001**	-0.19	0.01	0.05	-0.08	0.18	0.99
pericalcarine cortex	**-0.13**	**0.004**	**0.004**	-0.17	0.02	0.05	-0.07	0.22	0.99
postcentral gyrus	**-0.23**	**<0.001**	**<0.001**	-0.13	0.08	0.12	-0.04	0.49	0.99
posterior cingulate cortex	**-0.26**	**<0.001**	**<0.001**	-0.13	0.07	0.11	-0.07	0.21	0.99
precentral gyrus	**-0.23**	**<0.001**	**<0.001**	-0.12	0.10	0.14	0.00	0.95	0.99
precuneus	**-0.24**	**<0.001**	**<0.001**	-0.18	0.01	0.05	-0.02	0.78	0.99
rostral anterior cingulate cortex	**-0.28**	**<0.001**	**<0.001**	-0.18	0.02	0.05	0.01	0.80	0.99
rostral middle frontal gyrus	**-0.25**	**<0.001**	**<0.001**	-0.18	0.01	0.05	-0.03	0.65	0.99
superior frontal gyrus	**-0.31**	**<0.001**	**<0.001**	**-0.22**	**0.003**	**0.03**	0.00	0.97	0.99
superior parietal cortex	**-0.23**	**<0.001**	**<0.001**	**-0.24**	**0.001**	**0.03**	-0.03	0.59	0.99
superior temporal gyrus	**-0.26**	**<0.001**	**<0.001**	-0.12	0.12	0.15	-0.03	0.64	0.99
supramarginal gyrus	**-0.25**	**<0.001**	**<0.001**	-0.13	0.09	0.13	0.02	0.78	0.99
frontal pole	**-0.13**	**0.002**	**0.002**	-0.15	0.04	0.08	0.01	0.83	0.99
temporal pole	**-0.19**	**<0.001**	**<0.001**	-0.17	0.02	0.05	-0.07	0.22	0.99
transverse temporal gyrus	**-0.17**	**<0.001**	**<0.001**	-0.05	0.48	0.48	-0.06	0.33	0.99
insula	**-0.24**	**<0.001**	**<0.001**	-0.15	0.04	0.08	-0.10	0.08	0.99
total surface area	**-0.32**	**<0.001**	**<0.001**	**-0.22**	**0.00**	**0.03**	-0.03	0.65	0.99

Rows in bold are considered significant, surviving correction for multiple comparisons with FDR q-value<0.05.

ST10. Mega-analysis of case-control cortical thickness differences in the childhood subsample.

	Cohen's d (SE)	95% confidence interval	N controls	N ADHD	p-value	FDR p-value
banks of superior temporal sulcus	-0.06 (0.05)	-0.15 to 0.03	974	1000	0.18	0.33
caudal anterior cingulate cortex	-0.02 (0.04)	-0.10 to 0.07	1040	1079	0.70	0.77
caudal middle frontal gyrus	-0.07 (0.04)	-0.15 to 0.02	1047	1076	0.13	0.26
cuneus	-0.02 (0.04)	-0.10 to 0.07	1047	1076	0.65	0.77
entorhinal cortex	-0.09 (0.04)	-0.18 to -0.01	1014	1031	0.04	0.16
fusiform gyrus	**-0.17 (0.04)**	**-0.25 to -0.08**	**1044**	**1077**	**<0.001**	**0.003**
inferior parietal cortex	-0.08 (0.04)	-0.16 to 0.01	1043	1079	0.08	0.22
inferior temporal gyrus	-0.08 (0.04)	-0.17 to 0	1040	1065	0.06	0.21
isthmus cingulate cortex	0.02 (0.04)	-0.06 to 0.11	1041	1078	0.57	0.71
lateral occipital cortex	-0.10 (0.04)	-0.18 to -0.01	1048	1080	0.03	0.15
lateral orbitofrontal cortex	-0.05 (0.04)	-0.13 to 0.04	1047	1081	0.27	0.41
lingual gyrus	-0.08 (0.04)	-0.17 to 0	1046	1081	0.06	0.21
medial orbitofrontal cortex	0.02 (0.04)	-0.07 to 0.10	1040	1070	0.66	0.77
middle temporal gyrus	-0.07 (0.04)	-0.15 to 0.02	1001	1025	0.13	0.26
parahippocampal gyrus	**-0.15 (0.04)**	**-0.23 to -0.06**	**1041**	**1076**	**<0.001**	**0.008**
paracentral lobule	-0.09 (0.04)	-0.17 to 0	1047	1075	0.04	0.16
pars opercularis of inferior frontal gyrus	-0.07 (0.04)	-0.16 to 0.01	1044	1074	0.09	0.22
pars orbitalis of inferior frontal gyrus	-0.05 (0.04)	-0.13 to 0.04	1046	1081	0.28	0.41
pars triangularis of inferior frontal gyrus	0.00 (0.04)	-0.08 to 0.09	1048	1074	0.97	0.97
pericalcarine cortex	-0.04 (0.04)	-0.13 to 0.04	1045	1077	0.35	0.47
postcentral gyrus	-0.08 (0.04)	-0.16 to 0.01	1034	1059	0.08	0.22
posterior cingulate cortex	0.00 (0.04)	-0.09 to 0.08	1045	1077	0.97	0.97
precentral gyrus	**-0.16 (0.04)**	**-0.25 to -0.07**	**1040**	**1064**	**<0.001**	**0.003**
precuneus	-0.10 (0.04)	-0.18 to -0.01	1044	1080	0.02	0.15
rostral anterior cingulate cortex	0.06 (0.04)	-0.03 to 0.14	1039	1067	0.21	0.35
rostral middle frontal gyrus	-0.03 (0.04)	-0.12 to 0.05	1045	1079	0.48	0.62
superior frontal gyrus	-0.01 (0.04)	-0.09 to 0.08	1044	1074	0.83	0.88
superior parietal cortex	-0.07 (0.04)	-0.16 to 0.01	1045	1073	0.10	0.24
superior temporal gyrus	-0.05 (0.04)	-0.13 to 0.04	990	995	0.31	0.44
supramarginal gyrus	-0.07 (0.04)	-0.15 to 0.02	1039	1064	0.12	0.25
frontal pole	-0.02 (0.04)	-0.10 to 0.07	1047	1080	0.69	0.77
temporal pole	**-0.18 (0.04)**	**-0.27 to -0.10**	**1042**	**1075**	**<0.001**	**0.001**
transverse temporal gyrus	0.06 (0.04)	-0.03 to 0,14	1046	1078	0,21	0.35
insula	-0.09 (0.04)	-0.18 to -0,01	1043	1079	0,03	0.16
total thickness	-0.05 (0.04)	-0.14 to 0,03	1048	1081	0,25	0.40

Rows in bold are considered significant, surviving correction for multiple comparisons with FDR q-value<0.05

ST11. Mega-analysis of case-control cortical thickness differences in a tertile split of the group of children (4-14y).

	1st tertile age 4-9			2nd tertile age 10-11			3rd tertile 12-14		
	Cohen's d	**p-value**	**FDR p-value**	**Cohen's d**	**p-value**	**FDR p-value**	**Cohen's d**	**p-value**	**FDR p-value**
banks of superior temporal sulcus	-0.03	0.71	0.89	-0.12	0.12	0.38	-0.04	0.65	0.93
caudal anterior cingulate cortex	-0.09	0.26	0.84	0.04	0.63	0.83	0.00	0.98	0.99
caudal middle frontal gyrus	-0.05	0.51	0.89	-0.09	0.23	0.45	-0.08	0.29	0.75
cuneus	-0.05	0.57	0.89	-0.03	0.66	0.83	0.02	0.75	0.93
entorhinal cortex	-0.02	0.76	0.89	-0.10	0.20	0.45	-0.16	0.04	0.39
fusiform gyrus	-0.09	0.26	0.84	**-0.31**	**<0.001**	**0.002**	-0.14	0.07	0.39
inferior parietal cortex	-0.05	0.51	0.89	-0.12	0.13	0.38	-0.08	0.30	0.75
inferior temporal gyrus	-0.03	0.70	0.89	-0.18	0.02	0.16	-0.05	0.51	0.90
isthmus cingulate cortex	0.05	0.53	0.89	0.04	0.57	0.83	-0.02	0.82	0.93
lateral occipital cortex	-0.14	0.08	0.76	-0.13	0.10	0.38	-0.02	0.75	0.93
lateral orbitofrontal cortex	0.09	0.27	0.84	-0.12	0.13	0.38	-0.08	0.30	0.75
lingual gyrus	-0.13	0.10	0.76	-0.10	0.21	0.45	-0.02	0.80	0.93
medial orbitofrontal cortex	0.05	0.50	0.89	0.02	0.82	0.88	0.03	0.72	0.93
middle temporal gyrus	-0.01	0.87	0.96	-0.11	0.16	0.40	-0.07	0.34	0.80
parahippocampal gyrus	-0.07	0.38	0.84	-0.18	0.02	0.16	-0.15	0.04	0.39
paracentral lobule	-0.06	0.44	0.89	-0.08	0.31	0.55	-0.14	0.06	0.39
pars opercularis of inferior frontal gyrus	-0.07	0.39	0.84	-0.06	0.40	0.66	-0.09	0.24	0.75
pars orbitalis of inferior frontal gyrus	-0.04	0.60	0.89	-0.03	0.71	0.83	-0.04	0.63	0.93
pars triangularis of inferior frontal gyrus	0.01	0.91	0.96	0.01	0.95	0.95	-0.01	0.94	0.99
pericalcarine cortex	-0.08	0.30	0.84	0.02	0.83	0.88	-0.05	0.49	0.90
postcentral gyrus	-0.13	0.11	0.76	-0.03	0.68	0.83	-0.06	0.40	0.82
posterior cingulate cortex	0.00	0.99	0.99	0.03	0.68	0.83	0.00	0.97	0.99
precentral gyrus	-0.22	0.01	0.11	-0.16	0.04	0.27	-0.13	0.08	0.39
precuneus	-0.08	0.32	0.84	-0.14	0.07	0.33	-0.08	0.26	0.75
rostral anterior cingulate cortex	0.08	0.30	0.84	0.03	0.74	0.84	0.07	0.38	0.82
rostral middle frontal gyrus	-0.03	0.68	0.89	-0.03	0.66	0.83	-0.02	0.80	0.93
superior frontal gyrus	0.03	0.72	0.89	-0.01	0.91	0.94	-0.02	0.76	0.93
superior parietal cortex	-0.08	0.31	0.84	-0.05	0.52	0.83	-0.09	0.24	0.75
superior temporal gyrus	0.01	0.91	0.96	-0.11	0.16	0.40	-0.02	0.77	0.93
supramarginal gyrus	-0.01	0.93	0.96	-0.15	0.05	0.32	-0.06	0.46	0.89
frontal pole	-0.03	0.71	0.89	0.03	0.71	0.83	-0.02	0.75	0.93
temporal pole	-0.07	0.38	0.84	**-0.25**	**<0.001**	**0.02**	-0.23	0.002	0.07
transverse temporal gyrus	0.25	0.002	0.07	-0.08	0.32	0.55	0.00	0.99	0.99
insula	0.02	0.76	0.89	-0.09	0.23	0.45	-0.20	0.01	0.16
total thickness	-0.09	0.26	0.84	-0.12	0.13	0.38	-0.09	0.22	0.75

Note: the 1st tertile has 317 cases and 340 controls, the 2nd tertile has 356 cases and 365 controls, the 3rd tertile has 408 cases and 343 controls. p-values in bold are considered significant, surviving correction for multiple comparisons with FDR q-value<0.05.

ST12. Mega-analysis of case-control cortical thickness differences in the adolescent subsample.

Cortical region	Cohen's d (SE)	95% confidence interval	N controls	N ADHD	p-value	FDR p-value
banks of superior temporal sulcus	0.16 (0.07)	0.02 to 0.31	328	402	0.03	0.60
caudal anterior cingulate cortex	-0.05 (0.07)	-0.19 to 0.1	347	432	0.54	0.90
caudal middle frontal gyrus	-0.1 (0.07)	-0.24 to 0.04	345	432	0.17	0.87
cuneus	-0.01 (0.07)	-0.16 to 0.13	346	432	0.85	0.90
entorhinal cortex	-0.03 (0.07)	-0.17 to 0.12	331	415	0.70	0.90
fusiform gyrus	-0.03 (0.07)	-0.17 to 0.11	345	428	0.66	0.90
inferior parietal cortex	0.09 (0.07)	-0.05 to 0.23	345	429	0.24	0.87
inferior temporal gyrus	0.05 (0.07)	-0.09 to 0.19	336	408	0.50	0.90
isthmus cingulate cortex	0.02 (0.07)	-0.12 to 0.16	346	431	0.78	0.90
lateral occipital cortex	0.17 (0.07)	0.03 to 0.32	347	432	0.02	0.60
lateral orbitofrontal cortex	-0.12 (0.07)	-0.26 to 0.02	347	431	0.11	0.80
lingual gyrus	-0.03 (0.07)	-0.17 to 0.11	344	429	0.70	0.90
medial orbitofrontal cortex	0.01 (0.07)	-0.13 to 0.16	346	431	0.84	0.90
middle temporal gyrus	0.07 (0.08)	-0.07 to 0.22	323	389	0.35	0.90
parahippocampal gyrus	-0.05 (0.07)	-0.19 to 0.09	345	429	0.48	0.90
paracentral lobule	-0.08 (0.07)	-0.22 to 0.06	347	431	0.29	0.87
pars opercularis of inferior frontal gyrus	-0.03 (0.07)	-0.17 to 0.11	346	429	0.70	0.90
pars orbitalis of inferior frontal gyrus	0.03 (0.07)	-0.11 to 0.18	346	432	0.64	0.90
pars triangularis of inferior frontal gyrus	0.04 (0.07)	-0.11 to 0.18	347	431	0.64	0.90
pericalcarine cortex	-0.05 (0.07)	-0.19 to 0.09	347	431	0.49	0.90
postcentral gyrus	-0.01 (0.07)	-0.15 to 0.13	345	427	0.91	0.91
posterior cingulate cortex	-0.03 (0.07)	-0.17 to 0.11	347	432	0.71	0.90
precentral gyrus	-0.13 (0.07)	-0.27 to 0.01	344	425	0.08	0.80
precuneus	0.02 (0.07)	-0.13 to 0.16	347	431	0.83	0.90
rostral anterior cingulate cortex	-0.08 (0.07)	-0.22 to 0.06	346	430	0.28	0.87
rostral middle frontal gyrus	-0.02 (0.07)	-0.16 to 0.13	347	432	0.84	0.90
superior frontal gyrus	0.07 (0.07)	-0.08 to 0.21	347	431	0.37	0.90
superior parietal cortex	0.08 (0.07)	-0.06 to 0.22	347	430	0.30	0.87
superior temporal gyrus	0.08 (0.08)	-0.06 to 0.23	319	378	0.28	0.87
supramarginal gyrus	0.02 (0.07)	-0.12 to 0.17	343	426	0.74	0.90
frontal pole	-0.02 (0.07)	-0.16 to 0.12	347	432	0.76	0.90
temporal pole	-0.12 (0.07)	-0.26 to 0.02	345	428	0.11	0.80
transverse temporal gyrus	-0.08 (0.07)	-0.22 to 0.06	345	429	0.30	0.87
insula	0.01 (0.07)	-0.13 to 0.15	344	428	0.90	0.91
total thickness	0.01 (0.07)	-0.13 to 0.16	347	432	0.85	0.90

ST13. Mega-analysis of case-control cortical thickness differences in the adult subsample.

Cortical region	Cohen's d (SE)	95% confidence interval	N controls	N ADHD	p-value	FDR p-value
banks of superior temporal sulcus	0.01 (0.06)	-0.1 to 0.13	514	709	0.81	0.95
caudal anterior cingulate cortex	-0.11 (0.06)	-0.22 to 0	538	730	0.06	0.43
caudal middle frontal gyrus	-0.02 (0.06)	-0.13 to 0.09	539	733	0.74	0.95
cuneus	0.11 (0.06)	0 to 0.22	539	732	0.06	0.43
entorhinal cortex	-0.06 (0.06)	-0.18 to 0.06	479	670	0.33	0.88
fusiform gyrus	-0.01 (0.06)	-0.12 to 0.11	493	687	0.89	0.95
inferior parietal cortex	0.08 (0.06)	-0.03 to 0.19	538	730	0.17	0.55
inferior temporal gyrus	0 (0.06)	-0.12 to 0.11	493	683	0.97	0.97
isthmus cingulate cortex	0.04 (0.06)	-0.07 to 0.15	539	733	0.52	0.95
lateral occipital cortex	0.14 (0.06)	0.02 to 0.25	539	730	0.02	0.43
lateral orbitofrontal cortex	0.03 (0.06)	-0.09 to 0.14	539	733	0.66	0.95
lingual gyrus	0.11 (0.06)	-0.01 to 0.22	494	688	0.07	0.43
medial orbitofrontal cortex	-0.08 (0.06)	-0.19 to 0.03	539	731	0.17	0.55
middle temporal gyrus	0.02 (0.06)	-0.1 to 0.13	477	670	0.80	0.95
parahippocampal gyrus	0.1 (0.06)	-0.01 to 0.22	492	688	0.09	0.43
paracentral lobule	-0.01 (0.06)	-0.13 to 0.1	538	732	0.80	0.95
pars opercularis of inferior frontal gyrus	-0.01 (0.06)	-0.12 to 0.1	539	731	0.89	0.95
pars orbitalis of inferior frontal gyrus	-0.01 (0.06)	-0.12 to 0.11	539	732	0.92	0.95
pars triangularis of inferior frontal gyrus	-0.03 (0.06)	-0.14 to 0.08	538	732	0.60	0.95
pericalcarine cortex	0.04 (0.06)	-0.07 to 0.16	539	732	0.45	0.95
postcentral gyrus	0.05 (0.06)	-0.06 to 0.16	528	727	0.41	0.95
posterior cingulate cortex	-0.11 (0.06)	-0.22 to 0	539	733	0.05	0.43
precentral gyrus	-0.06 (0.06)	-0.17 to 0.05	537	729	0.29	0.84
precuneus	0.04 (0.06)	-0.07 to 0.15	539	732	0.46	0.95
rostral anterior cingulate cortex	-0.09 (0.06)	-0.2 to 0.03	535	730	0.14	0.54
rostral middle frontal gyrus	0.03 (0.06)	-0.08 to 0.14	538	733	0.63	0.95
superior frontal gyrus	-0.04 (0.06)	-0.15 to 0.08	535	730	0.54	0.95
superior parietal cortex	0.1 (0.06)	-0.01 to 0.21	539	730	0.08	0.43
superior temporal gyrus	0.04 (0.06)	-0.08 to 0.16	476	661	0.54	0.95
supramarginal gyrus	0.02 (0.06)	-0.09 to 0.14	535	728	0.67	0.95
frontal pole	0.08 (0.06)	-0.03 to 0.2	539	733	0.14	0.54
temporal pole	-0.02 (0.06)	-0.13 to 0.1	494	688	0.75	0.95
transverse temporal gyrus	-0.02 (0.06)	-0.13 to 0.1	494	688	0.79	0.95
insula	-0.01 (0.06)	-0.12 to 0.1	532	725	0.90	0.95
total thickness	0.02 (0.06)	-0.09 to 0.13	539	733	0.71	0.95

ST14. Mega-analysis of case-control cortical thickness differences in the total sample (children, adolescents and adults combined).

Cortical region	Cohen's d (SE)	95% confidence interval	N controls	N ADHD	p-value	FDR p-value
banks of superior temporal sulcus	0 (0.03)	-0.06 to 0.06	1816	2111	0.97	0.97
caudal anterior cingulate cortex	-0.04 (0.03)	-0.11 to 0.02	1925	2241	0.16	0.61
caudal middle frontal gyrus	-0.05 (0.03)	-0.11 to 0.01	1931	2241	0.09	0.45
cuneus	0.02 (0.03)	-0.04 to 0.08	1932	2240	0.44	0.86
entorhinal cortex	-0.08 (0.03)	-0.14 to -0.01	1824	2116	0.02	0.16
fusiform gyrus	**-0.1 (0.03)**	**-0.16 to -0.04**	**1882**	**2192**	**0.002**	**0.02**
inferior parietal cortex	0.01 (0.03)	-0.05 to 0.07	1926	2238	0.82	0.95
inferior temporal gyrus	-0.03 (0.03)	-0.09 to 0.03	1869	2156	0.30	0.75
isthmus cingulate cortex	0.03 (0.03)	-0.03 to 0.09	1926	2242	0.40	0.82
lateral occipital cortex	0.03 (0.03)	-0.03 to 0.09	1934	2242	0.33	0.78
lateral orbitofrontal cortex	-0.03 (0.03)	-0.09 to 0.03	1933	2245	0.29	0.75
lingual gyrus	-0.02 (0.03)	-0.08 to 0.04	1884	2198	0.58	0.92
medial orbitofrontal cortex	0 (0.03)	-0.06 to 0.06	1925	2232	0.90	0.95
middle temporal gyrus	-0.02 (0.03)	-0.08 to 0.05	1801	2084	0.60	0.92
parahippocampal gyrus	-0.06 (0.03)	-0.13 to 0	1878	2193	0.04	0.30
paracentral lobule	-0.05 (0.03)	-0.11 to 0.01	1932	2238	0.09	0.45
pars opercularis of inferior frontal gyrus	-0.04 (0.03)	-0.1 to 0.02	1929	2234	0.18	0.65
pars orbitalis of inferior frontal gyrus	-0.02 (0.03)	-0.08 to 0.04	1931	2245	0.58	0.92
pars triangularis of inferior frontal gyrus	0.01 (0.03)	-0.05 to 0.07	1933	2237	0.85	0.95
pericalcarine cortex	-0.01 (0.03)	-0.07 to 0.05	1931	2240	0.73	0.95
postcentral gyrus	-0.02 (0.03)	-0.08 to 0.04	1907	2213	0.57	0.92
posterior cingulate cortex	-0.03 (0.03)	-0.1 to 0.03	1931	2242	0.26	0.75
precentral gyrus	**-0.11 (0.03)**	**-0.18 to -0.05**	**1921**	**2218**	**<0.001**	**0.005**
precuneus	-0.03 (0.03)	-0.09 to 0.03	1930	2243	0.36	0.79
rostral anterior cingulate cortex	-0.01 (0.03)	-0.07 to 0.05	1920	2227	0.73	0.95
rostral middle frontal gyrus	0 (0.03)	-0.06 to 0.06	1930	2244	0.95	0.97
superior frontal gyrus	0 (0.03)	-0.06 to 0.07	1926	2235	0.89	0.95
superior parietal cortex	0.01 (0.03)	-0.05 to 0.08	1931	2233	0.65	0.95
superior temporal gyrus	0 (0.03)	-0.07 to 0.06	1785	2034	0.89	0.95
supramarginal gyrus	-0.02 (0.03)	-0.08 to 0.04	1917	2218	0.53	0.92
frontal pole	0.01 (0.03)	-0.05 to 0.07	1933	2245	0.79	0.95
temporal pole	**-0.12 (0.03)**	**-0.19 to -0.06**	**1881**	**2191**	**<0.001**	**0.003**
transverse temporal gyrus	0.01 (0.03)	-0.05 to 0.07	1885	2195	0.71	0.95
insula	-0.05 (0.03)	-0.11 to 0.01	1919	2232	0.14	0.61
total thickness	-0.04 (0.03)	-0.1 to 0.03	1934	2246	0.25	0.75

Rows in bold are considered significant, surviving correction for multiple comparisons with FDR q-value<0.05.

ST15. Validation of surface area results based on split halves of the data in the childhood subset.

	Validation Group 1				Validation Group 2			
Cortical region	**Cohen's d**	**N Controls**	**N Patients**	**FDR p-value**	**Cohen's d**	**N controls**	**N Patients**	**p-value**
banks of superior temporal sulcus	-0.15	479	484	0.03	-0.06	494	515	0.33
caudal anterior cingulate cortex	-0.09	511	527	0.21	-0.08	528	552	0.22
caudal middle frontal gyrus*	-0.19	512	525	0.01	-0.12	533	552	0.04
cuneus	-0.06	511	525	0.36	-0.07	534	550	0.23
entorhinal cortex	-0.05	494	503	0.44	-0.06	518	528	0.34
fusiform gyrus	-0.16	510	525	0.02	-0.10	532	550	0.09
inferior parietal cortex	-0.18	508	526	0.01	-0.07	532	552	0.24
inferior temporal gyrus	-0.12	507	522	0.09	-0.15	533	542	0.01
isthmus cingulate cortex	-0.18	511	529	0.01	-0.11	528	550	0.08
lateral occipital cortex	-0.16	513	527	0.02	-0.10	533	551	0.10
lateral orbitofrontal cortex*	-0.19	512	529	0.01	-0.17	534	552	0.006
lingual gyrus	-0.17	512	529	0.02	-0.03	534	552	0.68
medial orbitofrontal cortex	-0.22	506	520	0.005	-0.11	532	550	0.09
middle temporal gyrus*	-0.15	490	503	0.03	-0.13	510	521	0.04
parahippocampal gyrus	-0.07	509	525	0.34	-0.05	530	550	0.44
paracentral lobule	-0.08	513	525	0.24	-0.06	533	550	0.30
pars opercularis of inferior frontal gyrus	-0.19	511	524	0.01	0.00	532	550	0.95
pars orbitalis of inferior frontal gyrus	-0.10	512	529	0.13	-0.06	533	552	0.33
pars triangularis of inferior frontal gyrus	-0.16	513	524	0.02	-0.05	534	550	0.38
pericalcarine cortex	-0.04	512	528	0.56	-0.06	533	551	0.35
postcentral gyrus	-0.13	504	516	0.05	-0.08	527	544	0.20
posterior cingulate cortex*	-0.17	510	526	0.02	-0.16	531	552	0.008
precentral gyrus	-0.21	509	518	0.007	-0.02	531	546	0.74
precuneus	-0.20	510	529	0.008	-0.06	533	551	0.34
rostral anterior cingulate cortex*	-0.18	507	519	0.01	-0.17	533	548	0.007
rostral middle frontal gyrus	-0.16	511	528	0.02	-0.12	532	551	0.06
superior frontal gyrus*	-0.27	509	524	<0.001	-0.13	534	550	0.03
superior parietal cortex	-0.13	511	524	0.06	-0.13	533	549	0.03
superior temporal gyrus	-0.27	484	481	<0.001	-0.06	502	512	0.35
supramarginal gyrus	-0.21	507	518	0.007	-0.08	528	545	0.22
frontal pole	-0.04	512	529	0.53	-0.06	534	552	0.31
temporal pole	-0.10	509	527	0.15	-0.11	533	548	0.07
transverse temporal gyrus	-0.06	512	528	0.35	-0.08	533	550	0.22
insula	-0.17	509	527	0.02	-0.09	532	551	0.13
total surface area*	-0.27	513	529	<0.001	-0.16	534	552	0.009

*Indicate regions that show validation: P_{FDR}<0.05 in group1 and (uncorrected) p –value <0.05 in Group2

ST16. Validation of cortical thickness results based on split halves of the data in the childhood subset.

	Validation Group 1				Validation Group 2			
Cortical region	**Cohen's d**	**N controls**	**N Patients**	**FDR p-value**	**Cohen's d**	**N controls**	**N Patients**	**p-value**
banks of superior temporal sulcus	-0.11	478	484	0.33	-0.02	495	516	0.77
caudal anterior cingulate cortex	0.01	511	527	0.86	-0.05	528	552	0.46
caudal middle frontal gyrus	-0.09	512	525	0.33	-0.04	534	551	0.54
cuneus	-0.05	512	526	0.63	0.01	534	550	0.86
entorhinal cortex	-0.11	494	503	0.33	-0.08	519	528	0.19
fusiform gyrus*	-0.19	510	527	0.04	-0.14	533	550	0.02
inferior parietal cortex	-0.09	508	527	0.33	-0.06	534	552	0.32
inferior temporal gyrus	-0.06	507	522	0.58	-0.11	532	543	0.08
isthmus cingulate cortex	0.02	512	528	0.80	0.03	528	550	0.68
lateral occipital cortex	-0.15	513	528	0.13	-0.05	534	552	0.44
lateral orbitofrontal cortex	-0.04	512	529	0.63	-0.05	534	552	0.40
lingual gyrus	-0.08	511	529	0.36	-0.08	534	552	0.21
medial orbitofrontal cortex	0.02	507	520	0.80	0.01	532	550	0.85
middle temporal gyrus	-0.10	490	504	0.33	-0.04	510	521	0.54
parahippocampal gyrus	-0.16	509	526	0.13	-0.13	531	550	0.03
paracentral lobule	-0.10	513	525	0.33	-0.08	533	550	0.22
pars opercularis of inferior frontal gyrus	-0.09	511	524	0.36	-0.07	532	550	0.25
pars orbitalis of inferior frontal gyrus	-0.09	512	529	0.33	0.01	533	552	0.93
pars triangularis of inferior frontal gyrus	-0.02	513	524	0.86	0.02	534	550	0.77
pericalcarine cortex	-0.04	512	527	0.63	-0.04	532	550	0.55
postcentral gyrus	-0.10	505	514	0.33	-0.05	528	545	0.40
posterior cingulate cortex	0.04	512	525	0.63	-0.05	532	552	0.42
precentral gyrus	-0.12	509	518	0.33	-0.20	530	546	0.00
precuneus	-0.09	510	529	0.36	-0.11	533	551	0.07
rostral anterior cingulate cortex	0.04	507	519	0.63	0.06	531	548	0.33
rostral middle frontal gyrus	-0.03	511	528	0.80	-0.04	533	551	0.47
superior frontal gyrus	0.00	509	524	1.00	-0.02	534	550	0.80
superior parietal cortex	-0.11	511	524	0.33	-0.03	533	549	0.59
superior temporal gyrus	-0.05	485	481	0.63	-0.05	504	514	0.48
supramarginal gyrus	-0.07	508	518	0.51	-0.07	530	546	0.28
frontal pole	0.02	512	529	0.80	-0.06	534	551	0.33
temporal pole*	-0.19	509	527	0.04	-0.18	532	548	0.003
transverse temporal gyrus	0.08	512	528	0.39	0.03	533	550	0.65
insula	-0.06	509	528	0.58	-0.13	533	551	0.03
total thickness	-0.10	513	529	0.33	-0.07	534	552	0.26

*Indicate regions that show cross validation: $P_{FDR}<0.05$ in group1 and (uncorrected) p-value<0.05 in Group2

ST17. Interaction between age-group and diagnostic status for validated cortical regions.

Cortical region	p-value for the term Dx*Agegroup
Surface area	
caudal middle frontal gyrus	0.28
lateral orbitofrontal cortex	0.23
middle temporal gyrus	0.44
posterior cingulate cortex	0.65
rostral anterior cingulate cortex	0.19
superior frontal gyrus	0.04
total surface area	0.14
Thickness	
fusiform gyrus	0.03
temporal pole	0.32

ST18. Exploration of Diagnosis-by-sex interaction effect on validated cortical regions in the childhood subset.

Cortical region	p-value Diagnosis*Sex in the main model
Surface area	
caudal middle frontal gyrus	0.93
lateral orbitofrontal cortex	0.40
middle temporal gyrus	0.64
posterior cingulate cortex	0.30
rostral anterior cingulate cortex	0.79
superior frontal gyrus	0.96
total surface area	0.99
Thickness	
fusiform gyrus	0.41
temporal pole	0.81

Note: Diagnosis= case or control

ST19. IQ sensitivity analysis for ADHD affected cortical surface area regions in the childhood subset.

Cortical region	Cohen's *d* Dx	n controls/ patients	p-value Dx	Cohen's d Dx	n controls/ patients	Pvalue IQ	p-value Dx
Surface area							
caudal middle frontal gyrus	-0.15	1040/1079	<0.001	NA	974/1009	0.21	NA
lateral orbitofrontal cortex	-0.17	1047/1081	<0.001	-0.16	975/1014	<0.001[a]	0.006
middle temporal gyrus	-0.13	1001/1024	0.004	NA	929/958	0.06	NA
posterior cingulate cortex	-0.16	1042/1078	<0.001	NA	970/1010	0.06	NA
rostral anterior cingulate cortex	-0.16	1041/1067	<0.001	NA	967/1000	0.51	NA
superior frontal gyrus	-0.19	1044/1074	<0.001	-0.19	972/1007	0.03	<0.001
total surface area	-0.21	1048/1081	<0.001	-0.20	976/1014	0.001	<0.001
Thickness							
fusiform gyrus	-0.17	1044/1077	<0.001	NA	972/1008	0.10	NA
temporal pole	-0.18	1042/1075	<0.001	NA	970/1008	0.76	NA

[a]IQ was nominal significant in the model and therefore the effect size and p-value for diagnosis (Dx) is given for the model including IQ. NA= not applicable.

ST20. Frequency of comorbid disorders and medication use in the childhood subset of cases.

	Answer	Count	Percentage
Ever diagnosed with a psychiatric comorbidity?	No	308	28.5
	Yes	194	17.9
	Unknown	579	53.6
Ever diagnosed with a mood disorder?	No	443	41.0
	Yes	13	1.2
	Unknown	625	57.8
Ever diagnosed with an anxiety disorder	No	417	38.6
	Yes	39	3.6
	Unknown	625	57.8
Ever diagnosed with ODD?	No	407	37.7
	Yes	79	7.3
	Unknown	595	55.0
Ever used stimulants as treatment for ADHD	No	167	15.4
	Yes	271	25.1
	Unknown	643	59.5
Currently using Stimulants as treatment for ADHD	No	465	43.0
	Yes	258	23.9
	Unknown	723	66.9

Note: Please see ST2 for the instruments used per cohort

ST21. Effects of presence of comorbid disorders and medication use on affected cortical regions in the childhood ADHD subsample with available comorbidity and medication data.

	Uncorrected p-values from the model with age, sex, site and either of the comorbidity or medication factors.					
Cortical region	**Comorbidity ever**	**Mood disorder ever**	**Anxiety disorder ever**	**ODD ever**	**Stimulants ever[a]**	**Stimulants current[b]**
Surface area						
caudal middle frontal gyrus	0.98	0.37	0.34	0.83	0.60	0.70
lateral orbitofrontal cortex	0.16	0.10	0.76	0.54	0.54	**0.04**
middle temporal gyrus	0.92	0.15	0.66	0.76	0.90	0.45
posterior cingulate cortex	0.96	0.09	0.10	0.08	0.57	0.22
rostral anterior cingulate cortex	0.08	0.36	0.31	0.91	0.26	**0.03**
superior frontal gyrus	0.73	0.22	0.39	0.63	0.78	0.17
total surface area	0.44	0.07	0.56	0.85	0.44	0.06
Thickness						
fusiform gyrus	**0.02**	0.63	0.32	0.74	0.53	0.35
temporal pole	0.07	0.25	0.21	0.55	0.77	0.84

* nominal significant at $p<0.05$ [a]The group that had ever used stimulants did not differ from those that had never used stimulants on ADHD severity scores (total number of ADHD symptoms), p=0.64, (these analysis were done only in those with ADHD symptom scores available $n_{ever}=13$, $n_{never}=51$). [b]The group that currenly used stimulants did not differ from those that were currently not using stimulant medication on ADHD severity scores (total number of ADHD symptoms), p=0.62 , (these analysis were done only in those with ADHD symptom scores $n_{\text{current users}}=13$, $n_{\text{currently not using stimulants}}=120$).

ST22. Correlation of affected cortical regions with ADHD symptoms in childhood subsample of cases with available symptom ratings.

Cortical region		Hyperactive/Impulsive Symptoms Conners		Inattention Symptoms Conners	
	N	Pearson's r	p-value	Pearson's r	p-value
Surface area					
caudal middle frontal gyrus	240	-0,10	0,16	0.03	0.67
lateral orbitofrontal cortex	240	-0.06	0.41	0.01	0.89
middle temporal gyrus	240	-0.01	0.83	0.08	0.22
posterior cingulate cortex	240	-0.02	0.76	0	0.95
rostral anterior cingulate cortex	240	-0.18	**0.01**[a]	-0.06	0.38
superior frontal gyrus	240	-0.19	**0.01**[a]	-0.03	0.63
total surface area	240	-0.15	**0.03**[a]	0.02	0.72
Thickness					
fusiform gyrus	240	0.09	0.17	0.10	0.13
temporal pole	240	0.02	0.72	0.06	0.35

The largest group of cases with a similar ADHD symptom rating instrument were cases with Conners ratings . These subjects are from ACPU, ADHD200KKI, ADHD200NYU, ADHD200OHSU, UCHZ and Barcelona. Correlations are partial correlations, controlling for age/gender, site, and ICV. The latter only in the surface area correlations [a]correlation between cortical surface area and number of symptoms is nominal significant at $p<0.05$.

ST23. Familiality analysis of cortical regions affected in ADHD in the Neuroimage dataset.

Cortical region	N controls/sibs/ADHD	p-value unaffected sibs versus control
Surface area		
caudal middle frontal gyrus[a]	120/175/211	<0.001
lateral orbitofrontal cortex[a]	120/175/211	0.002
middle temporal gyrus	95/175/156	0.014
posterior cingulate cortex	120/175/211	0.23
rostral anterior cingulate cortex	119/175/211	0.03
superior frontal gyrus[a]	120/175/211	<0.001
total surface area[a]	120/175/211	0.003
Thickness		
fusiform gyrus	120/175/211	0.02
temporal pole	120/175/211	0.24

[a]regions showing a familial effect at P< 0.01 surviving multiple comparisons (M_{eff} corrected threshold).

ST24. Comparison of AIC and BIC for (curvi-)linear model fits in the Generation-R sample.

Cortical region	model	AIC	BIC
Surface area			
caudal middle frontal gyrus	linear	34176	34228
	quadratic	34174	34231
	cubic	34175	34238
lateral orbitofrontal cortex	linear	33853	33905
	quadratic	33849	33906
	cubic	33847	33911
middle temporal gyrus	linear	34822	34874
	quadratic	34814	34871
	cubic	34816	34879
posterior cingulate cortex	linear	30469	30521
	quadratic	30467	30525
	cubic	30468	30531
rostral anterior cingulate cortex	linear	29516	29567
	quadratic	29514	29571
	cubic	29516	29579
superior frontal gyrus	linear	38531	38582
	quadratic	38529	38587
	cubic	38530	38594
total surface area	linear	48615	48667
	quadratic	48609	48667
	cubic	48611	48674
Thickness			
fusiform gyrus	linear	-4034	-3982
	quadratic	-4037	-3979
	cubic	-4036	-3973
temporal pole	linear	1751	1803
	quadratic	1749	1807
	cubic	1751	1814

ST25. Sensitivity analyses of associations between surface area and CBCL syndrome scale attention problems adjusting for additional covariates in Generation-R.

Additional Covariate	Cortical region	B	SE	CI_{Lower}	CI_{Upper}	β	p-value	FDR p-value
IQ[a]	caudal middle frontal gyrus	-12.54	5.51	-23.35	-1.72	-0.034	0.023	0.027
	middle temporal gyrus	-13.07	5.89	-24.63	-1.51	-0.029	0.027	0.027
	total surface area	-304.23	77.88	-456.93	-151.53	-0.034	<0.001	<0.001
ADHD Medication[b]	caudal middle frontal gyrus	-12.96	5.66	-24.06	-1.85	-0.035	0.022	0.033
	middle temporal gyrus	-12.12	6.04	-23.97	-0.28	-0.027	0.045	0.045
	total surface area	-298.49	79.90	-455.17	-141.81	-0.033	<0.001	0.001
MRI Scanner Software[c]	caudal middle frontal gyrus	-13.83	5.48	-24.57	-3.09	-0.038	0.012	0.017
	middle temporal gyrus	-13.59	5.86	-25.08	-2.10	-0.030	0.020	0.020
	total surface area	-318.84	77.16	-470.14	-167.53	-0.036	<0.001	<0.001
Image quality[d]	caudal middle frontal gyrus	-13.16	5.46	-23.87	-2.45	-0.036	0.016	0.024
	middle temporal gyrus	-11.75	5.74	-23.01	-0.48	-0.026	0.041	0.041
	total surface area	-292.77	75.06	-439.95	-145.59	-0.033	<0.001	<0.001

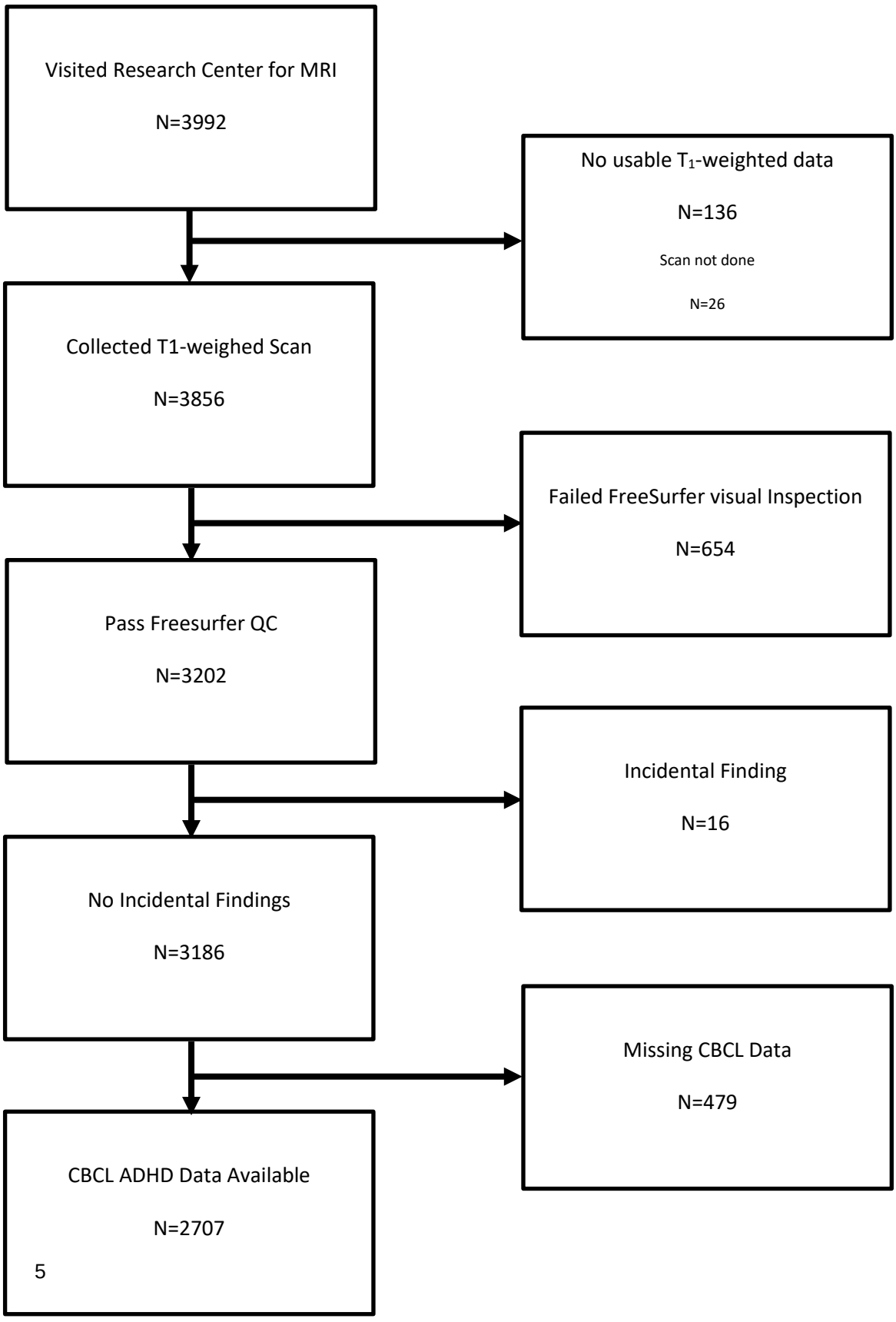
Note: Regions are the average of left and right hemisphere surface area, and are the regions showing significant group differences in split-half analyses (**ST13&ST14**) and a significant association in primary continuous analyses in the population-based cohort. Model is adjusted for age, sex, ethnic background, ICV, and the additional covariate listed in the first column "Additional covariate". B is the unstandardized regression coefficient for the square root transformed CBCL syndrome scale attention problems score, and CI is the 95% confidence interval of that regression coefficient. β is the standardized regression coefficient. [a]IQ= non verbal IQ. [b]ADHD medication=yes or no using an ADHD medication. [c]MRI scanner software is DV23 or DV24. [d]Image quality = T1-weighted scan quality.

ST26. Correlations between automated T_1-weighted image quality metric and sample characteristics in Generation-R.

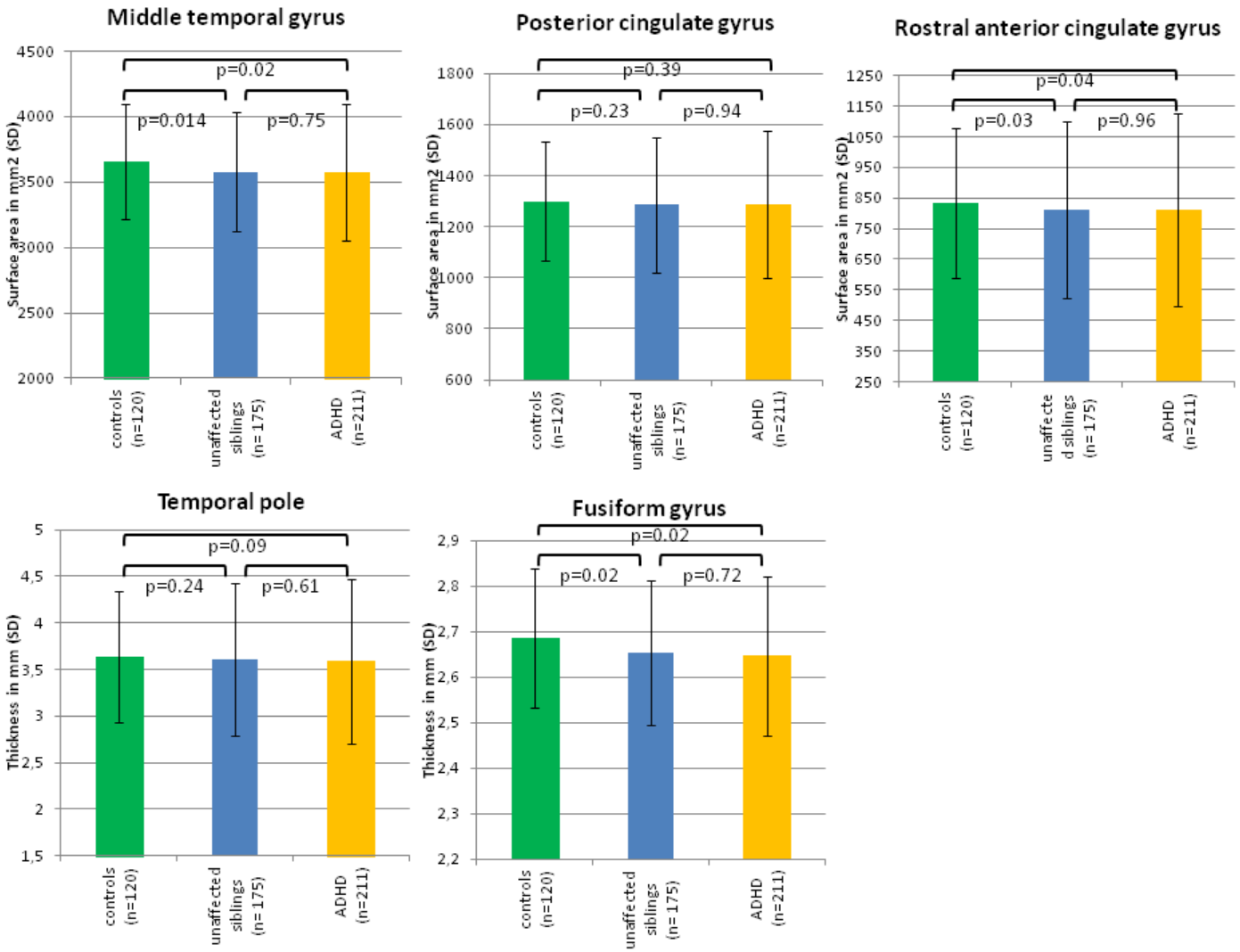
		Spearman's ρ	*p*	Kendall's τ	*p*
All T_1-weighted scans (n=3960)	Age at MRI	0.108	<0.001	0.072	<0.001
	CBCL Attention problem Scale	-0.050	0.004	-0.035	0.004
	CBCL ADHD problem Scale	-0.053	0.002	-0.038	0.002
Usable FreeSurfer output (n=2707)	Age at MRI	0.0923	<0.001	0.062	<0.001
	CBCL Attention problem Scale	-0.026	0.179	-0.018	0.181
	CBCL ADHD problem Scale	-0.023	0.241	-0.016	0.241

Correlation coefficients represent the correlation with the automated T1-weighted quality metric. All T1-weighted scans represent all individuals who have a T1-weighted MRI and CBCL assessment, which includes those who were excluded due to poor FreeSurfer image reconstruction. Usable Freesurfer output refers to the actual study sample used for analyses. Regarding motion, in the full sample, prior to excluding imaging data not suitable for analysis, more motion artifact was correlated with higher levels of attention problems (n=3329, r = -0.05 , p = 0.004), though this association disappeared in the sample used for analysis (n=2707, r = -0.03, p = 0.18) indicative of both an effective quality control in excluding unusable data and minimal residual confounding of motion-related artifact in analyses.

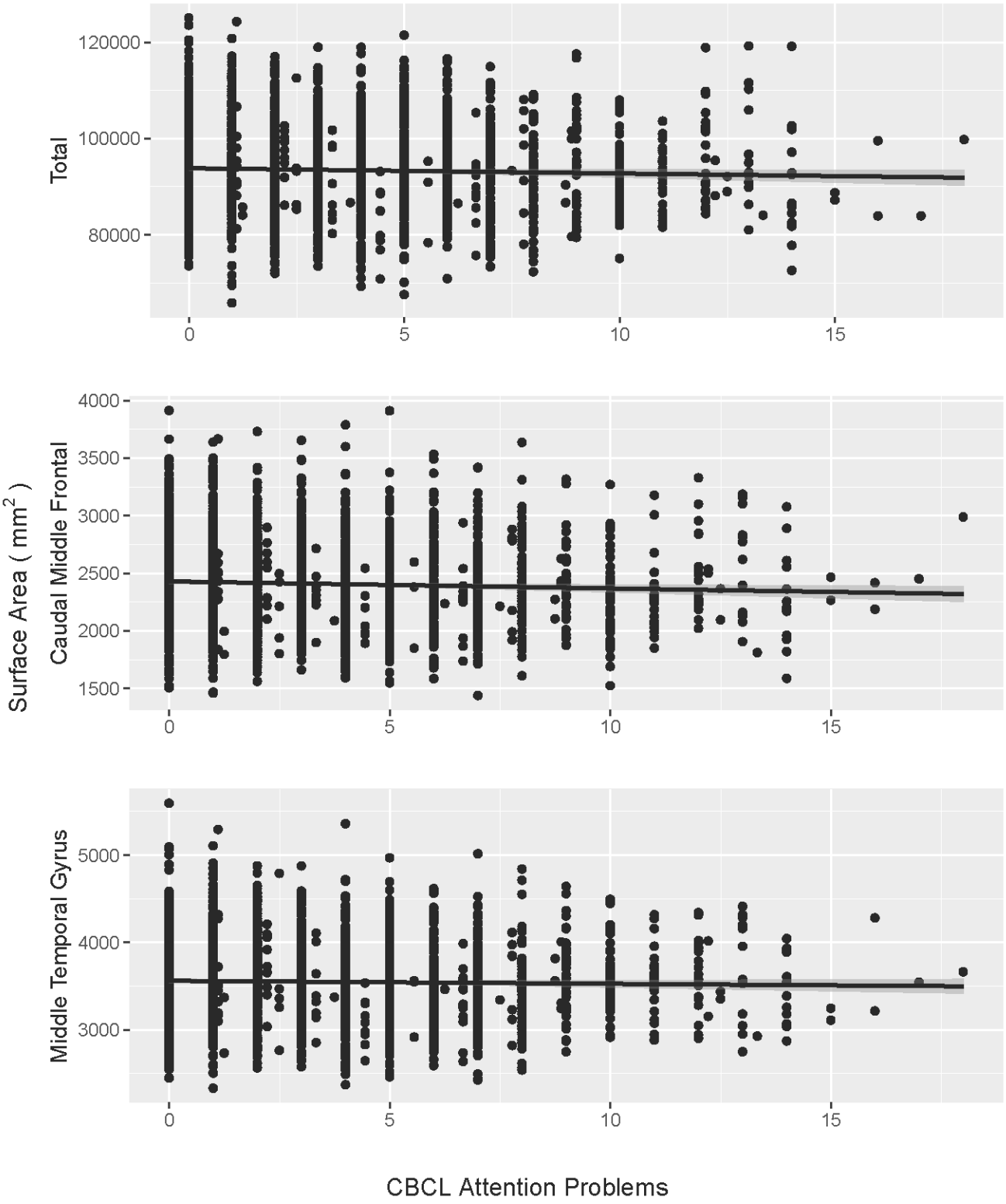
SF1. Flowchart of inclusion in the Generation-R sample


Visited Research Center for MRI
N=3992
No usable T_1-weighted data
N=136
Scan not done
N=26
Collected T1-weighed Scan
N=3856
Failed FreeSurfer visual Inspection
N=654
Pass Freesurfer QC
N=3202
Incidental Finding
N=16
No Incidental Findings
N=3186
Missing CBCL Data
N=479
CBCL ADHD Data Available
N=2707

SF2. Bar graphs showing effects of familiality on the ADHD- affected cortical regions the Neuroimage datasets (n=506), supplement to Figure 2.



SF3. Scatterplots of attention problem scores from the CBCL against surface area measures in Generation R.



Note: Displayed are the CBCL attention problem scores plotted against the surface area regions that were significantly associated with the attention scores (main manuscript Table 3).

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